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ABSTRACT

Over the past 20 years, alcohol researchers have made intensive efforts to understand alcohol use and its outcomes. To date, researchers have made much progress toward understanding the causes and consequences of alcoholism and its related problems. This publication attempts to convey the great spirit and promise of alcohol research. Established findings that serve as foundations for future research are presented, and compelling areas for the coming decade that promise to advance understanding of the nature of alcoholism and promote efforts to prevent and treat the disease are highlighted. Extensive illustrations and photographs supplement the text. From the discussions of the health, social, and economic consequences of alcohol abuse and alcoholism that motivate the study of alcohol-related problems, to the presentation of new research concepts and technologies that enhance the systematic analysis of those problems, this document testifies to the ability of alcohol researchers ultimately to resolve one of our country's foremost public health problems. Chapters are: (1) Alcohol Abuse and Alcoholism; (2) Alcohol and the Brain; (3) Genetics and Environment; (4) Why Do People Drink?; (5) The Medical Consequences of Alcoholism; (6) Fetal Alcohol Syndrome; (7) Prevention and Treatment. An additional chapter contains information on developing new medications for alcoholism. (JBJ)

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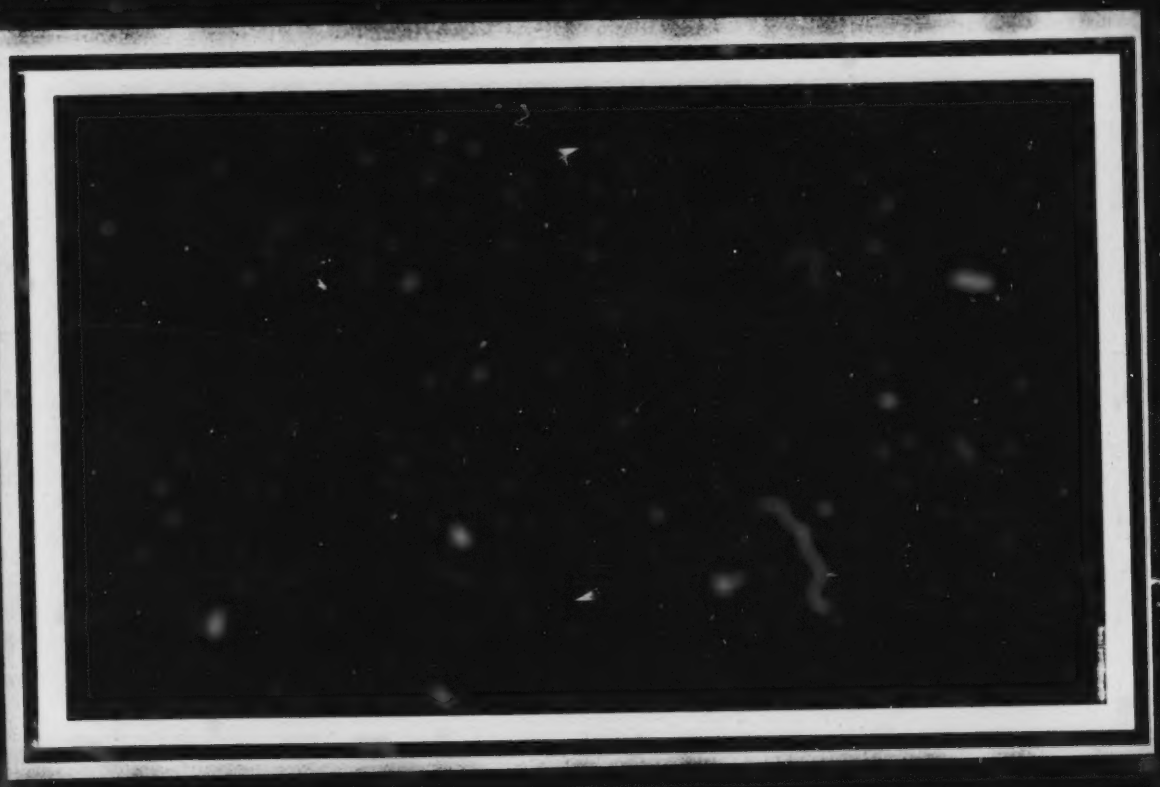

Alcohol Research

Promise for the Decade

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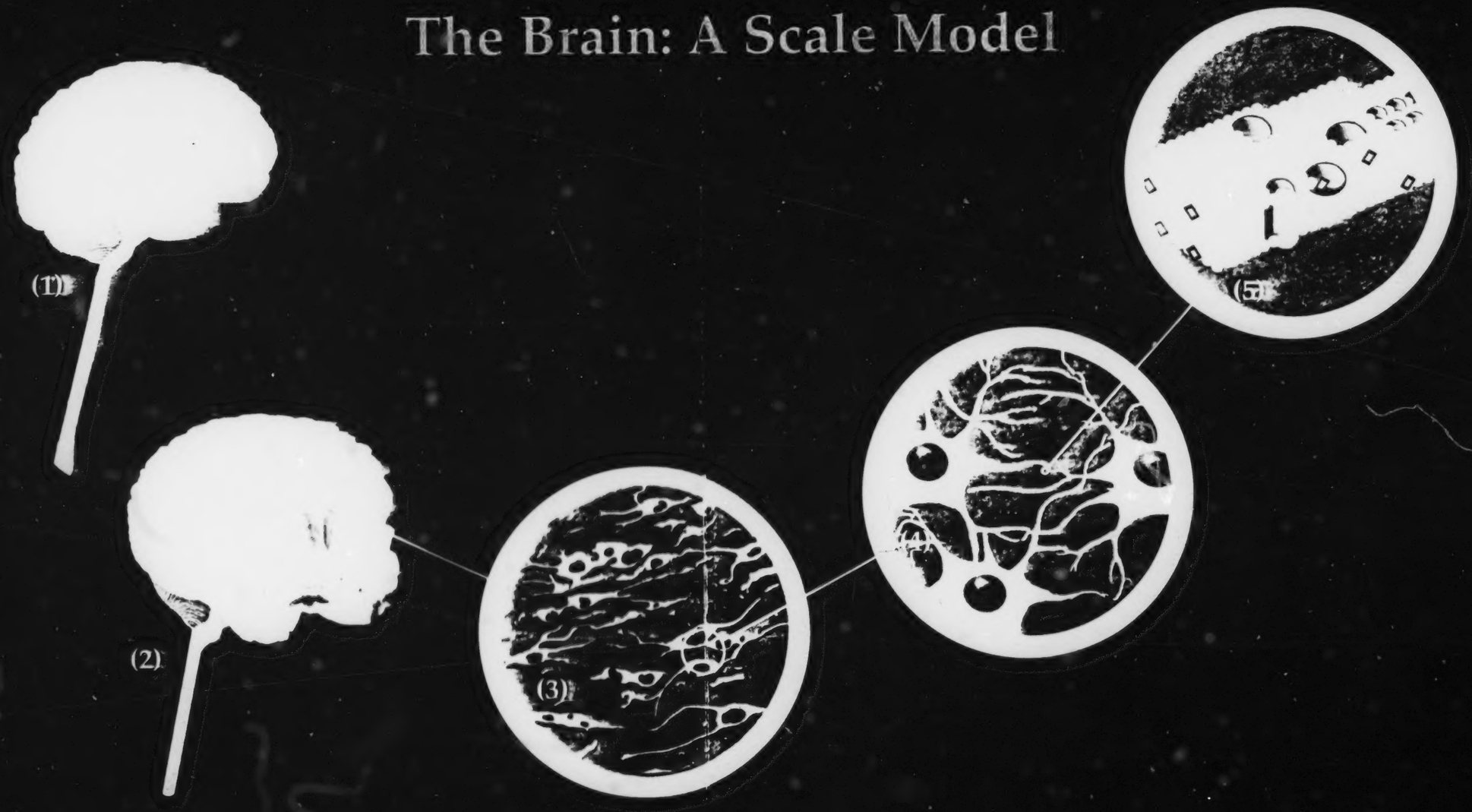

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ALCOHOL RESEARCH: PROMISE FOR THE DECADE

Enoch Gordis, M.D.
Director
National Institute on Alcohol
Abuse and Alcoholism
August 1991

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
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ALCOHOL RESEARCH: PROMISE FOR THE DECADE

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FOREWORD

The importance of research on alcohol abuse and alcoholism is unmistakable in light of the substantial harm and costs that result from these disorders. The debilitating effects of alcohol on the physical and social well-being of problem drinkers, the far-reaching harm that drinking causes in our communities, the related costs borne by individuals and society alike—each of these consequences affirms the need for greater knowledge about what causes alcoholism, how it can be prevented, and—once a drinking problem develops—how it can be treated effectively. Such knowledge will come only from research.

Over the past 20 years, alcohol researchers have made intensive efforts to understand alcohol use and its outcomes. During this time, the alcohol research field has developed from relatively modest beginnings to become one of the most rapidly growing areas of scientific investigation. To date, alcohol researchers have made much progress toward understanding the causes and consequences of alcoholism and its related problems.

As we move toward the beginning of a new century, alcohol research has a preeminent goal: to gather knowledge that will enhance the development of methods to prevent and to treat alcohol use disorders.

Developing new medications to advance alcoholism treatment is critical to this process. As part of the continuing pursuit of enhanced treatment measures, researchers now are extending the search to include new pharmacotherapies that target the mechanisms of the addiction itself. Scientists are armed in this quest with increasing knowledge about the brain processes underlying addiction. The discovery of new medications will offer fresh hope to those who struggle to achieve and maintain long-term sobriety. Some of these

new drugs may ease the intense craving for alcohol experienced by many recently abstinent alcoholics or improve alcohol-induced cognitive impairments that can affect a patient's potential to benefit from traditional therapies.

It is unlikely that a single agent will be developed to treat this complex disease. However, coupling pharmacotherapies that control specific clinical events in the disease course with traditional behavioral and verbal therapies will enhance treatment outcome immeasurably.

Refined therapies will benefit many people. For alcohol dependent individuals, who face the realistic fear of relapse to drinking, improved interventions can abate—and, optimally, prevent—relapse occurrences and halt continuing disease that ultimately can lead to death. For society, which carries the weight of the enormous economic and social costs of problem drinking, improved treatment strategies that heighten the potential for long-term abstinence can lessen this burden and enhance overall quality of life. New therapies promise to reduce the billions of dollars lost annually from reduced workplace productivity, alcohol-related injuries and illnesses, and alcohol-related premature deaths. Furthermore, more effective treatment can reduce the frequency of the various social tragedies—motor vehicle crashes, falls, drownings, fires and burns, crime and family violence—that are associated with alcohol misuse.

While studies of the causes, prevention, and treatment of alcohol addiction are critical, investigations of the medical consequences of alcoholism continue to be key components in the research agenda. The severe disorders that develop from alcohol's damage to the body are responsible for great suffering and contribute substantially to the high cost of health care among alcoholic patients. Yet, scientists have observed that these pathologies are not distributed equally throughout the alcoholic population. Recent studies suggest that different underlying genetic factors in people exposed to high levels of alcohol may be responsible for the development of such disorders as fetal alcohol syndrome, liver cirrhosis, and Wernicke-Korsakoff's syndrome.

Future studies potentially can identify the physiological bases for genetic susceptibility to alcohol-related pathologies. Such knowledge can help scientists to develop specific techniques to prevent the onset of alcohol-related illnesses. In addition, this knowledge can enable clinicians to identify individuals at risk for developing these disorders, allowing for early identification of alcohol-related pathologies. Finally, knowledge of the etiologies of genetically-influenced consequences can augment efforts to generate more effective therapies for such disorders. Ultimately, these advances can effect large reductions in health care costs and save countless lives.

Two primary prerequisites must be met to accomplish the fundamental goals of alcohol research. First and foremost, the alcohol field needs the abiding efforts of talent d clinicians and researchers who, through complementary endeavors, link research advances and treatment practice. Second, the production of techniques and technologies that allow for the observation and evaluation of relevant phenomena are vital to research progress.

Animal models are a principal example of techniques needed in the coming decade of alcohol research. Developing models with correlate features of the human disease, such as craving or tolerance, will enable scientists to probe the biochemical and physiological mechanisms underlying these features. In turn, the animal models can serve as fundamental tools for developing and assessing treatment measures for the various elements of alcoholism.

As one of the first steps in medications development, animal studies can ensure that further tests can be conducted in humans without danger. Nonetheless, animal studies alone cannot confirm the efficacy of potential pharmacological therapies in alcoholism treatment. Clinical trials of new pharmacotherapies are indispensable for determining dose, efficacy, and safety of medications in humans. Such trials will serve as integral tools for developing new medications for alcoholism treatment.

Advances in technology also will enhance the research efforts in the next 10 years. During the past decade, a number of noninvasive imaging techniques—computerized tomography, magnetic resonance imaging, positron emission tomography, electroencephalography—were enhanced. These techniques offer scientists the unprecedented and exciting opportunity to look inside the living brain without invading the brain. In the coming decade, alcohol researchers will be able to apply these powerful resources to probe the actions of alcohol on the biochemistry and physiology of the living brain.

Imaging studies are likely to reveal critical knowledge about the brain mechanisms involved in the fundamental components of alcohol addiction. In addition, by allowing the opportunity to view the possible changes in the brain that precede the onset of symptoms, imaging technology will contribute much to the development of successful prevention measures. These tools eventually may be used in conjunction with treatment research and practice, enabling researchers to observe the alterations in brain physiology that occur in

response to various behavioral and pharmacological treatments.

At present, the scarcity of imaging technology frequently restricts its use in many laboratory and clinical alcohol studies. Given the potential value of this technology in alcohol research, the alcohol research community increasingly will turn to these new tools and apply strategies that will foster their efficient use.

The research areas highlighted here are just a few of the many exciting components of alcohol research. *Alcohol Research: Promise for the Decade* presents the established findings that serve as foundations for future research and highlights the compelling areas for the coming decade that promise to advance understanding of the nature of alcoholism and promote efforts to prevent and treat the disease. This document attempts to convey the great spirit and promise of alcohol research. From the discussion of the health, social, and economic consequences of alcohol abuse and alcoholism that motivate the study of alcohol-related problems, to the presentation of new research concepts and technologies that enhance the systematic analysis of those problems, this document testifies to the ability of alcohol researchers ultimately to resolve one of our country's foremost public health problems.

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Director
National Institute on Alcohol
Abuse and Alcoholism

ACKNOWLEDGMENTS

It is always easier to look backward and record what has happened than to look forward and authoritatively describe what can be. In this regard, we were most fortunate to have the help of a group of truly farsighted individuals whose expert knowledge of science and keen insights about the future potential of alcohol research were instrumental in shaping this report.

Guiding the Institute's response to the Congress were members of the NIAAA Extramural Science Advisory Board (ESAB), who determined NIAAA's approach to the task, invited the scientific papers that formed the basis for the document, and reviewed the work as it progressed. Core members of the ESAB who were involved in this process included James D. Beard, Ph.D., Professor of Psychiatry and Director, Alcohol Research Center, Memphis, Tennessee; Ting-Kai Li, M.D., Distinguished Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; Barbara S. McCrady, Ph.D., Professor and Clinical Director, Rutgers Center of Alcohol Studies, Piscataway, New Jersey; and Robin Room, Ph.D., Scientific Director, Alcohol Research Group, Berkeley, California. Permanent liaison members to the ESAB representing the National Advisory Council on Alcohol Abuse and Alcoholism included Martha B. Alexander, Executive Director, Charlotte Council on Alcoholism and Chemical Dependency, Charlotte, North Carolina, and member of the Board of Directors for the National Council on Alcoholism and Other Drug Dependencies; Bernell N. Boswell, Executive Director, The Cottage Program International, Inc., Salt Lake City, Utah; and Roger Meyer, M.D., Professor and Chairman, Department of Psychiatry and Director, Alcohol Research Center, University of Connecticut Medical School, Farmington, Connecticut. Samuel B. Guze, M.D., Professor and Chairman, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, served as liaison from the National Institute of Mental Health Extramural Science Advisory Board.

Five additional distinguished scientists served as consultants to aid NIAAA's ESAB in this project: Henri Begleiter, Ph.D., Professor of Psychiatry, State University of New York Health Science Center at Brooklyn, New York, New York; Floyd Bloom, M.D., Director, Research Institute, Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic, La Jolla, California; Harold Holder, Ph.D., Director, The Prevention Research Center, Berkeley, California; Marcus A. Rothschild, M.D., Chief,

Radioisotope Service, Veterans Administration Medical Center, New York, New York; and G. Terence Wilson, Ph.D., Graduate School of Applied Professional Psychology, Rutgers University, Piscataway, New Jersey.

Altogether, more than 30 biomedical and psychosocial scholars contributed their thoughts and insights through papers that aided the ESAB and our writers in developing the perspectives that are the foundations of this report. To each of these individuals, members of the ESAB, and special consultants, go our thanks for their expert knowledge and guidance, and our gratitude for their patience as we sought their counsel time and again throughout the development of this document.

Finally, special thanks are due to the NIAAA staff who have worked so diligently to produce *Alcohol Research: Promise for the Decade:* Kenneth Warren, Ph.D., Director of the NIAAA Office of Scientific Affairs, whose leadership sustained this effort from its conceptual stages to its publication; Michael Lewis, Ph.D., Executive Secretary of NIAAA's Extramural Science Advisory Board, who coordinated the initial efforts in the development of the document; Barbara Smothers, Ph.D., in NIAAA's Office of Scientific Affairs, whose conceptualizations, writing, and editing helped to ensure the document's accuracy and readability; Ann M. Bradley, also in the Office of Scientific Affairs, who contributed substantively and editorially to the final document; Brenda G. Hewitt, Special Assistant to the Director, who, from inception to completion, imbued the report with excitement about the potential of alcohol research to better individual lives and societal conditions; and Jane C. Lockmuller, M.S., Office of Scientific Affairs, who, with exceptional fortitude and skill, wrote and crafted the final version of the report that you are about to read. Without her diligence, *Alcohol Research: Promise for the Decade* would be a lesser document.

I ALCOHOL ABUSE AND ALCOHOLISM

What are alcohol abuse and alcoholism? Although many adults drink with few, if any, problems, others experience a number of adverse consequences from drinking. Even isolated episodes of alcohol misuse may result in such tragic consequences as alcohol poisoning and injury or death from alcohol-impaired driving and other accidents. When alcohol problems persist over time, however, they are classified as one of two clinical disorders: alcohol abuse or alcoholism.

Today, alcoholism is recognized as a disease characterized by abnormal alcohol-seeking behavior that results in impaired control over drinking. Variously termed "alcohol dependence," "alcohol addiction," and "alcoholism" over the years, this disease has four main clinical features: craving, impaired control over drinking, physical dependence, and tolerance. These are the key elements of what has been termed the "alcohol dependence syndrome."

Physicians long have witnessed the reality of craving in recovering patients for whom the notion of having a drink becomes overwhelming and preoccupying, impossible to ignore. This craving for alcohol—a drug hunger—often occurs in recently abstinent alcoholics and is an important determinant of relapse to drinking. The basis of this critical element of alcoholism has not been determined. Some researchers suggest that it is an appetitive urge, similar to hunger, with a physiological foundation. Others submit that the desire to drink is a behavioral response to environmental triggers. Recent research demonstrating that alcoholics display numerous physical responses when exposed to alcohol suggests that craving, indeed, has a physical basis.

Whereas craving refers to the hunger for alcohol before drinking begins, impaired control over drinking refers to the difficulty that an alcoholic experiences in stopping once drinking

Alcohol abuse and alcoholism are clinical disorders that affect millions of Americans of every age, race, and sex. Although these disorders cost our society billions of dollars annually, the human costs are immeasurable. Photographs courtesy of Lloyd Wolfe.

has started. Unlike nonproblem drinkers, alcoholics may lack internal signals that would allow them to regulate alcohol intake.

Physical dependence is an adaptive state manifested by intense physical disturbances that occur when drinking is discontinued. A consequence of chronic alcohol use, physical dependence results from the adaptation of central nervous system structures and functions (and probably those of other organs) to the presence of alcohol. Dependence necessitates continued drinking to prevent alcohol withdrawal syndrome, a host of symptoms ranging from profound anxiety, tremulousness ("the shakes"), intense hyperactivity, and sleep disturbances, to hallucinations and seizures. The intensity of such symptoms reflects the level of physiological dependence on alcohol.

During withdrawal, some alcoholics experience only mild symptoms, whereas others endure extremely severe reactions that can be life-threatening. Whether mild or severe, these symptoms can prompt a return to drinking to relieve the discomfort. Thus, it is important to control the more severe withdrawal reactions in alcoholics who are beginning abstinence. Recent evidence suggests that repeated untreated withdrawals from alcohol may have a cumulative brain-damaging effect, possibly leading to more serious withdrawal episodes in the future.

An individual who drinks heavily over a period of months or years gradually develops an ability to consume increasing amounts of alcohol without showing gross signs of intoxication. This phenomenon, called tolerance, often is mistaken to be a sign of resistance to the adverse consequences of heavy drinking. Actually, the tolerance to alcohol that occurs after chronic heavy drinking is indicative of long-lasting changes produced by alcohol. Tolerance allows individuals to maintain higher blood alcohol concentrations without appearing intoxicated; yet, many aspects of brain functioning are impaired and vital organs may be damaged.

Any drinking that produces a problem, whether social or medical, mild or severe, is important. "Alcohol abuse" refers to problem drinking—short of the alcohol dependence syndrome—that results in health consequences, social problems, or both. "Problem drinking" and "nondependent alcohol abuse" are additional terms that have been used to describe this problematic use of alcohol. While alcohol abusers are not dependent on alcohol, they nonetheless may experience social and medical problems as a result of poor judgment or unconcern about the adverse consequences of their drinking.

Problems caused by even occasional drinking episodes (such as an isolated alcohol-related traffic crash or a fall while intoxicated) can be serious or fatal. Continuous heavy drinking can provoke more severe social problems, such as divorce and other family problems, and economic problems, such as job loss. In addition, such serious medical consequences as liver cirrhosis, memory loss, stroke, heart damage, and cancer may occur.

Although alcohol abusers and alcoholics suffer from many of the same health, social, and economic problems, dependence on alcohol and the impaired ability to control alcohol intake that characterize alcoholism distinguish the two disorders. Social use does not inevitably progress to alcohol abuse or to alcoholism. Rather, over the course of time, persons who abuse alcohol can become social users or abstainers later in life; those who abstain in their youth or young adulthood may become alcohol abusers as they age. Further, an individual can be an alcohol abuser without being alcoholic, or can be alcoholic before displaying alcohol-related social and medical problems.

The Extent of the Problem

More Americans use alcohol than any other drug, including cigarette tobacco. According to national surveys, approximately two-thirds of all adults in the United States drink alcoholic beverages. Of individuals who drink, one-half are light drinkers and one-half are moderate to heavy drinkers. However, some individuals drink far more than others; the 10 percent of those who drink most heavily account for fully one-half of all alcohol consumed in this country.

More men than women drink, and more men than women are heavy drinkers. White Americans are more likely to use alcohol than African-Americans, American Indians, and Asian Americans. Nonetheless, with the exception of Asian Americans, members of U.S. minority groups suffer to a greater extent from alcohol-related problems than do white Americans. For example, among men and women, nonwhite individuals experience higher death rates than white individuals from alcoholic cirrhosis. Among the homeless population, it is estimated that 20 to 45 percent suffer from alcohol problems.

During the 1980s, alcohol use by high school seniors began a welcome, though gradual, downward trend. Yet, alcohol use among young people is still alarmingly high. In 1990, 32 percent of high school seniors reported having five or more consecutive drinks on a single occasion during the 2-week period prior to the survey.

Consequences of Alcohol Use

Alcohol use may lead to social consequences that often affect not only the drinker but also family, friends, and strangers. For example, alcohol can play an important role in accidents, including falls and motor vehicle crashes. The seriousness of this issue is reflected in acci-

dent statistics: Accidents account for the majority of deaths among people between the ages of 5 and 34 years in the United States. Over one-half of these deaths are due to traffic accidents, and alcohol has been implicated in recent years in about one-half of the estimated 46,000 annual traffic deaths.

The percentage of teenagers who die in traffic accidents continues to be a matter of public concern. Approximately 40 percent of all teenage deaths each year result from traffic crashes. Yet, evidence suggests that alcohol may be decreasing as a factor in teenage traffic crashes. From 1982 through 1988, the percentage of teenage drivers who were intoxicated in fatal crashes decreased by 36 percent. Although this trend is encouraging, alcohol is involved in a substantially greater number of fatal crashes among teenage drivers than among other age groups.

It is estimated that alcohol is a factor in approximately 30 percent of all suicides and, in particular, that alcohol use is prevalent among adolescents who commit suicide. In one study, researchers found that, between 1978 and 1983, 46 percent of adolescents who took their own lives had been drinking just before committing their final act. Alcohol also appears to play a significant role in suicides that are impulsive rather than premeditated. The use of alcohol is predominant among suicide victims who used firearms to take their lives.

In the United States, the social and economic toll of alcohol abuse and alcoholism far exceeds the toll of many other contemporary medical and social problems. Alcohol abuse and alcohol dependence affect about 10 percent of adult Americans. Heavy alcohol use contributes to medical problems; one study found that an estimated 25 percent of all persons admitted to general hospital beds screened positively for alcoholism. Further, the social costs of alcohol problems match the high economic costs.

Virtually every organ (for example, liver, pancreas, heart, and brain) and every system (for example, gastrointestinal, reproductive, and endocrine) in the human body can be damaged by chronic drinking. The damage can lead to a variety of diseases and other health problems. These medical consequences of alcohol abuse and alcoholism are responsible for a significant amount of illness in the United States and result in at least 40,000 deaths annually.

Alcohol abuse and alcoholism are costly. For 1985, the total economic cost of alcohol abuse and alcoholism was estimated at $70.3 billion; this estimate was projected to $85.8 billion for 1988. Of the projected 1988 total, $33.0 billion (38.4 percent) was due to lost employment and reduced productivity (an indirect cost that is difficult to measure) and $28.5 billion (33.2 percent) was due to premature mortality. The projected cost of treatment and associated research, training, and other supportive activities was relatively low: $8.7 billion (10.2 percent).

On the average, health care costs for untreated alcoholics are at least 100 percent greater than those for nonalcoholics. Alternatively, treating alcoholism reduces general health care costs. One study reported that the average monthly health care costs for an alcoholic's family were 50 to 90 percent lower following treatment of the alcoholic family member.

Why study alcohol use? Because by studying alcohol use, we can learn how to prevent alcohol abuse and alcoholism and how to minimize their effects when they do occur. In turn, by learning how to control alcohol abuse and alcoholism, we can decrease health care costs and reduce the incidence of heart disease, cancer, liver disease, accidental injuries, suicide, crime, and violence. In short, by studying alcohol use, we can make a difference.

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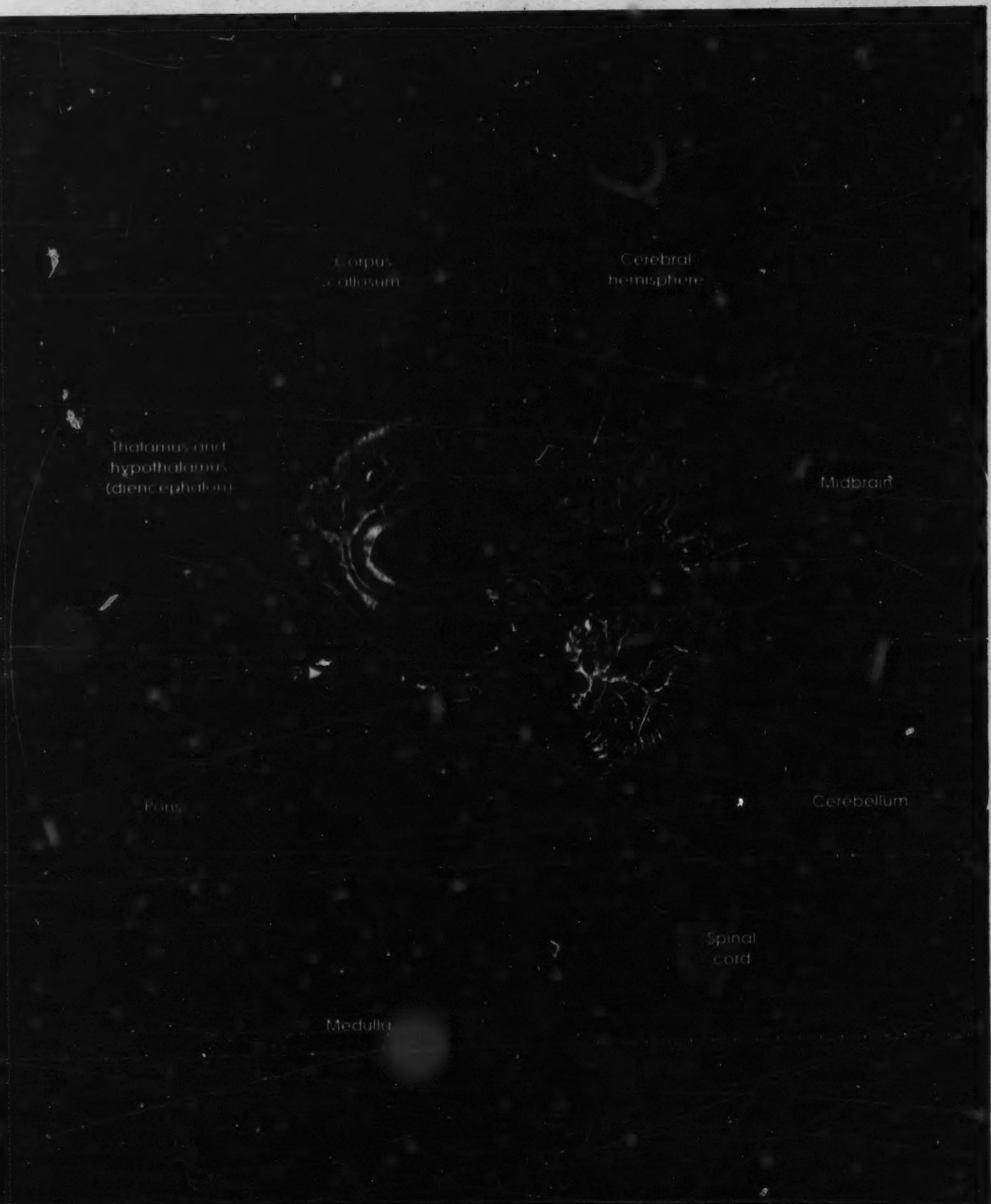
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II ALCOHOL AND THE BRAIN

Clinicians long have been aware of the myriad medical consequences that can develop from alcohol use. Liver disease, pancreatitis, and degenerative changes in heart and muscle are all examples of alcohol-induced damage. Yet, the effects of alcohol that produce intoxication, reinforcement of continued drinking, and the features of the disease process of alcoholism are based principally in the brain.

Neuroscience is the field of study that focuses on the structure and activities of the brain. Through research in this field, we have come to learn that the brain governs a host of basic responses such as fear and pain, hunger and thirst. Moreover, it is the seat of all that is human—thinking, abstracting, emotions, planning for the future, and memories of the past.

It is not surprising that neuroscience is an especially important area of investigation for alcohol researchers. Alcoholism appears to involve changes in mood, behavior, and possibly appetite, all of which are governed by the brain. Accordingly, neuroscience research provides essential information in the search for why some people who drink become addicted to alcohol and how alcohol damages normal brain functions.

Researchers have identified many of the fundamental questions concerning the effects of alcohol on the brain, and new research methods and technologies are becoming available every day to advance our search for answers. Neuroscience research promises to propel us through the next decade to an exciting—and in many ways unprecedented—age of discovery about the activities and functions of the brain and their role in alcohol abuse and alcoholism.

The ways in which alcohol affects different types of nerve cells in different parts of the brain are just beginning to be understood. Illustration by Robert Czechowski.

The Brain: Neurons and Networks

The brain is one of the most complex organs in the body. Functioning basically as a communication center, its highly organized systems control thinking and feeling, process information from the senses, guide muscular movement, and regulate body functions.

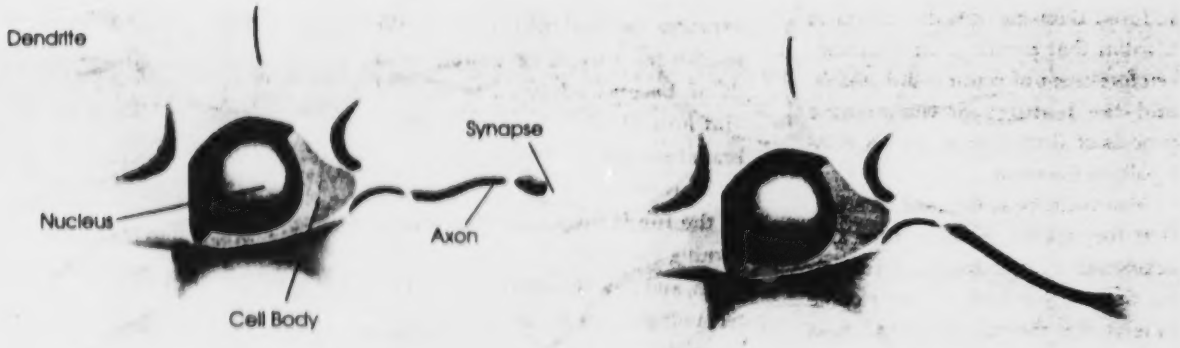
Nerve cells, or neurons, are the basic units of the brain and nervous system. Although their structure is similar to that of other cells, neurons are specialized to communicate by transmitting messages. Some nerve cells outside the brain—in particular the sensory neurons of the eyes, ears, nose, tongue, and skin—generate signals in response to such external stimuli as light and sound; others transmit signals that control muscle activity. The neurons of the brain receive information from the sensory organs, send messages that control the muscles in body movement, and generate thoughts, feelings, and actions.

Throughout the brain, each of the billions of neurons makes as many as thousands of connections with its neighbors. As the brain controls thoughts and behaviors, it must integrate large amounts of diverse, rapidly received information from many groups of these neurons in various brain regions. This is an ever-changing situation, involving vast numbers of neurons that often function simultaneously within specific systems of the brain. The study of these systems of neurons, or neural networks, has emerged as a major area of research.

The actions of neurons and neural networks control mental activity. Even as you read this sentence, thousands of neurons are "firing," exchanging messages that enable you to see the symbols on the page, understand them, and incorporate the information into your memory. These basic actions also allow you to consider new ideas and to respond with emotions and opinions.

How do neurons actually communicate? Each nerve cell bears a large number of highly branched filaments called dendrites and one long filament called an axon. The dendrite receives a chemical message from an adjacent neuron. The chemical message is converted into an impulse that involves the movement of electrically charged elements (ions), such as sodium and potassium, through the cell membrane. This bioelectric current travels along the length of the axon, where the message is picked up by dendrites of neurons farther away.

For the most part, nerve cells actually do not touch each other. Rather, a tiny gap known as a synapse separates the axon of the transmitting neuron from the dendrite of the receiving neuron. As the nerve impulse reaches the end of the axon, chemical messengers, or neurotransmitters, carry the message across the synapse.



Each nerve cell bears highly branched filaments called dendrites and a single long filament called an axon. The synapse is the space between the axon of one nerve cell and the dendrite of another.

Approximately 100 neurotransmitters and neuromodulators (other chemicals that modify the function or effects of a neurotransmitter) have been identified. These chemical messengers are released from the terminal portion of the axon, cross the synapse, and bind to specific receptors (proteins that serve as sites of attachment) on the surface of the dendrite. Just as the shape of a lock determines the fit of a key, the shape of the receptor allows it to bind a precise neurotransmitter. The binding of a neurotransmitter to an appropriate receptor sets off a cascade of events within the receiving neuron. These events stimulate the receiving neuron to send an electric current down its own axon, inducing chemical changes associated with the formation of thoughts, emotions, or memories. Complex machinery within the cell—various enzymes, molecules known as second messengers, minerals such as calcium, and so-called coupling proteins that link the various components—carry out these processes.

The Effects of Alcohol on the Brain

Why is it important for alcohol researchers to study neurons and neural networks? We study the cellular events that underlie the brain's response to alcohol because this research will explain the basic chemical and physiological processes that are the foundation of alcohol addiction. Moreover, our studies provide invaluable information about the basic functioning of the brain itself.

The functions of the brain are accomplished through an intricate interplay of numerous brain systems. To grasp a true picture of the sundry effects of alcohol on the brain, we must explore alcohol's actions at each of the many levels of functional organization: the single neuron, cell-to-cell communication, and integrated neuron activities within brain systems. Many studies focus on the most basic level—the individual neuron and the effects of alcohol on the neuron's ability to transmit electrical signals through its cell membrane. Cellular studies also probe the effects of alcohol on neurotransmitters and neuromodulators—their production and release by certain neurons and their binding to receptors on others. Studies of higher organizational levels explore the effects of alcohol on the physiology of an isolated single neuron, on the composite activity of neurons within neural systems, and on the whole brain structure and function as measured through electrophysiology and behavior.

The Effects of Alcohol on Cellular Communication

Clearly, alcohol has a profound effect on the brain. Nevertheless, scientists still do not understand how alcohol can exert its effects to produce such phenomena as intoxication, reinforcement, tolerance, and dependence.

Because the brain exists principally as a communication system, it is assumed that alcohol acts to alter communication. Changes in communication may result from alcohol's actions on one or more levels of the brain's functional organization.

Studies of alcohol's actions on neurons—the basic unit of the brain—can provide important information about how alcohol disrupts the communication process. As a message, conveyed as a bioelectric signal, travels down the membrane, it stimulates the release of neurotransmitters from nerve endings. In turn, neurotransmitters act as chemical messengers that cross the gap (synapse) between

cells to carry the message to neighboring neurons. Studies of alcohol's actions on the communication process examine alcohol's effects on each of these stages: the communication of a signal within the neuron, the release of neurotransmitters from one neuron, and the binding of neurotransmitters to the neuron receiving a message. Further, because the critical events involved in the message transmission occur in the membrane of the neuron, scientists are examining whether alcohol alters communication by modifying the membrane's chemical and physical structure.

Investigators use electrophysiological techniques to uncover some of the mysteries surrounding alcohol's effects on the brain's communications systems. These procedures enable scientists to study the capacity of the neural membrane to propagate its bioelectric signal. Recently, the development of several new and innovative techniques has enhanced researchers' facility for examining these electrophysiological events.

One such procedure, known as voltage clamp recording, is a detailed and painstaking process in which a scientist, while looking through a microscope, inserts the tip of a fine microelectrode into a single cell. This technique allows researchers to measure varying current across the cell membrane resulting from alcohol-induced changes in the flow of ions through the membrane. "Tear-off patch clamping," a more recent technique, permits an even closer look at the effect of alcohol on ion movement across the membrane. This procedure can measure electrical events associated with ions moving through a single ion channel (a protein that both creates a pore in the membrane and controls the passage of ions into and out of the cell).

Studies using these and similar techniques have demonstrated that various brain regions differ in their sensitivity to alcohol. These approaches also have shown that alcohol can stimulate or hamper neuron functioning, depending on the type of neuron (that is, which receptors are present on the membrane of the nerve cell) and the brain region in which the neurons are found. In addition, alcohol may affect more than one type of ion channel and may increase or decrease ion flow through these membrane pores.

Studies have demonstrated that various brain regions differ in their sensitivity to alcohol.

Over the next few years, researchers will attempt to define the conductive mechanisms in different brain regions that are altered by alcohol. Once these mechanisms are defined, changes in the processes of message transmission that occur with chronic exposure to alcohol can be measured. Findings from such studies can help to relate the electrophysiological effects of alcohol on specific brain regions to the various behavioral actions associated with drinking.

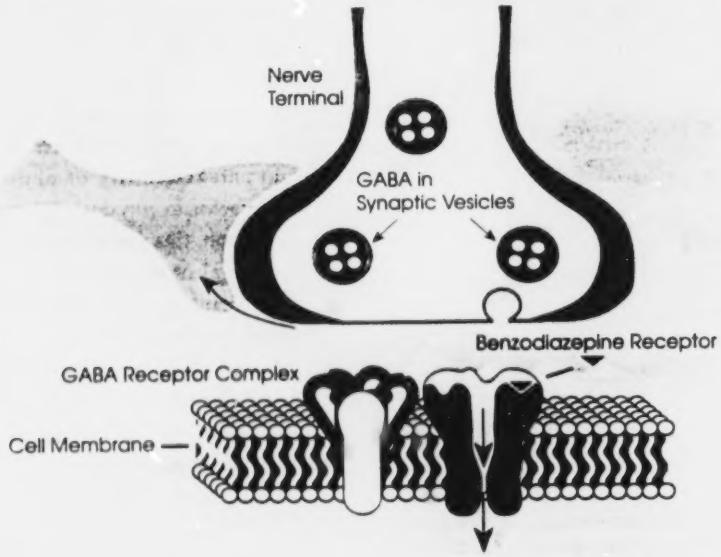
Neurotransmitters and Receptors

A neuron must be able to transmit a signal from one end of the cell to the other as well as interact with a wide array of other neurons. Because neurons do not actually touch each other, they must use a communication mechanism that can bridge the synapse that lies between adjacent cells.

Intercellular communication involves the release of neurotransmitters, an event stimulated by a bioelectric signal within the cell. The neurotransmitter crosses the synapse and binds to a receptor in the membrane of a neighboring cell. With the binding, the neighboring cell may become stimulated to fire or may become less responsive to other neurotransmitters. Accordingly, neurotransmitters serve to excite or to inhibit the firing of neighboring neurons. Because some neurotransmitters may act to modulate the message of other neurotransmitters, they are referred to as neuromodulators.

Alcohol is a psychotropic drug—a pharmacologic agent that alters brain function. Many psychotropic drugs, such as opiates, marijuana, and benzodiazepine tranquilizers, affect the brain by interacting with specific receptors on brain cell membranes. Alcohol, however, differs from these psychotropic drugs because it does not bind to one specific receptor. Rather, alcohol may act on distinctive receptors in the brain, and its actions may be unique for each receptor or, further, for each neurotransmitter system.

Because alcohol may act on receptors and generate specific effects depending upon the receptor involved, studying alcohol's actions on the brain is an extraordinarily complex challenge for researchers. To define and understand the specific behaviors that stem from the effects of alcohol on the brain, scientists must determine how alcohol exerts its actions on the cell surface receptors with which it interacts. Scientists, likewise, must ascertain how many of the more than 100 known neurotransmitters are involved in the expression of alco-



Molecules of gamma-aminobutyric acid (GABA) released into a synapse bind to receptors embedded in the surface of a nerve cell. This binding tends to bring about an inhibition of the nerve cell's activity. Alcohol and benzodiazepines (such as the tranquilizer Valium) exert some of their effects at this receptor.

hol's actions. At present, researchers have found evidence that a few neurotransmitter systems appear to be extremely sensitive to alcohol, including gamma-aminobutyric acid (GABA), glutamate, and serotonin.

GABA

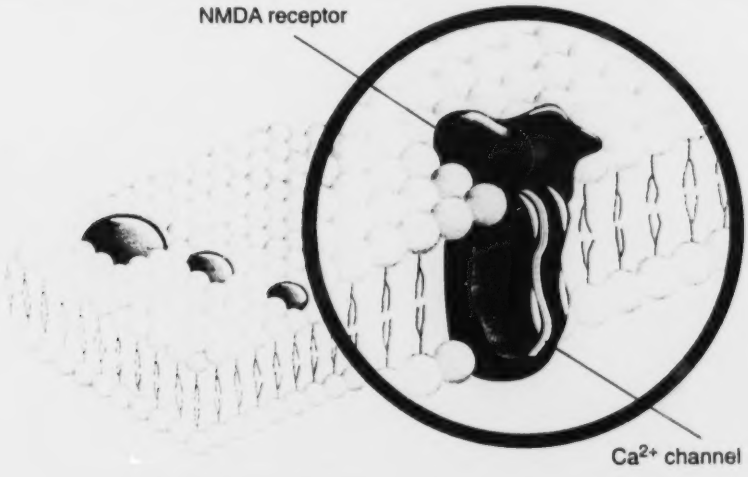
GABA is the major inhibitory neurotransmitter within the central nervous system. As an inhibitory neurotransmitter, the binding of GABA to its receptor on a neuron will dampen, or decrease, the ability of that neuron to propagate its bioelectric signal, or to fire.

The GABA receptor is actually a complex of several protein subunits. Within this protein complex, there is a specific binding site for the GABA molecule. The binding of GABA to its receptor causes chloride ions to enter the cell. This process makes it more difficult for the neuron to fire, rendering the neuron less sensitive to the effects of other neurotransmitters.

The GABA receptor also possesses a site that can bind drugs of the benzodiazepine class. Some benzodiazepines, such as the tranquilizer diazepam (Valium), further inhibit the ability of the neuron to fire. Other benzodiazepines, however, produce the opposite effect and may even cause seizures.

Scientists have begun to question how alcohol specifically affects the GABA receptor. It appears that the influence of alcohol on the GABA receptor is analogous to that of the benzodiazepines that function as tranquilizers. Alcohol seems to enhance the movement of chloride ions across the cell membrane and reduce the ability of the receiving neuron to fire.

Two effects attributed to alcohol—the reduction of anxiety and the loss of motor coordination associated with intoxication—may arise from the actions of alcohol on the GABA system, specifically its actions at the GABA receptor. At present, researchers are focusing their efforts on studying alcohol's interactions with GABA in the areas of the brain that appear sensitive to the effects of alcohol.



The neurotransmitter glutamate, acting at the NMDA receptor, is involved in learning, memory formation, and nerve cell development. Alcohol interferes with the function of this receptor, possibly contributing to memory disorders, impaired nervous system development, and alcohol withdrawal seizures. Courtesy of Dr. Boris Tabakoff.

In addition, scientists are focusing on identifying the characteristics of the GABA receptor that render it sensitive to alcohol. The configuration of different GABA subunits in select brain areas may contribute to alcohol's varying effects on different brain regions. Findings from these studies may pave the way for genetic research exploring why some people differ in their response to alcohol.

Tolerance to alcohol's sedative effects may result from an adaptive response of ion channels controlled by GABA to the chronic presence of alcohol. Studies using neurons taken from animals made tolerant to the sedative effects of alcohol have shown that the stimulatory effect of alcohol on GABA-controlled chloride ion channels in these cells is either reduced or absent.

Glutamate and NMDA

Whereas GABA is the major inhibitory neurotransmitter in the brain, glutamate is the major excitatory brain neurotransmitter, accounting for approximately 40 percent of all the nerve signals sent throughout the brain. When glutamate binds to its receptor on a neuron, it augments the potential of that neuron to fire. A number of distinct subtypes of glutamate receptors are named for various chemical analogs (substances that also specifically bind to these receptors). Alcohol primarily affects the receptor subtype named after the synthetic chemical N-methyl-D-aspartate, abbreviated NMDA. The binding of glutamate or NMDA to this receptor heightens the neuron's responsiveness to stimuli. At this receptor, glutamate has been implicated in such phenomena as learning and memory formation and is involved in neuronal development.

Evidence suggests that the NMDA receptor may be involved in the development of physical dependence on alcohol. Under normal conditions, activation of the NMDA receptor allows calcium ions to flow through ion channels into the cell, thereby causing the cell to become excited. Short-term exposure to alcohol inhibits NMDA-stimulated calcium flow and, consequently, dampens the cell's responsiveness. When the brain is exposed chronically to alcohol, however, it begins to compensate for this effect: The number of NMDA-activated ion channels in the brain increases. This adaptive process (known as upregulation) could result in hyperexcitability of neurons, a major factor in physical dependence. In addition, this process may account for several of the chronic effects of heavy drinking, including alcohol-withdrawal seizures.

Alcohol can impair memory and learning processes, as well as produce profound cognitive problems. Recently, scientists have found evidence that glutamate and the NMDA receptor may play a significant role in these damaging alcohol-induced effects. This area of research is compelling, given the suggested role of the glutamate and the NMDA receptor in normal memory functions. Knowledge of the interaction between alcohol and the NMDA receptor can help us to understand more fully the memory impairments that result from heavy drinking, including the phenomenon of blackouts.

Serotonin

Evidence suggests that serotonin, a neurotransmitter involved in mood, sleep, and consummatory behavior, also may be sensitive to alcohol. Researchers have used serotonin-uptake blockers—substances that block brain serotonin uptake and allow for greatly increased action of the neurotransmitter—to analyze the role of serotonin in alcohol consumption. They have found that serotonin-uptake blockers appear to diminish somewhat the desire for alcohol in some alcoholics, a possible indication of the role of serotonin in alcohol consumption. These findings could have considerable importance in future development of medications to control craving for alcohol.

Much of our knowledge of neurotransmitters and receptors has been attained through studies using genetic animal models of alcoholism. Animal models are important research tools because they allow for controlled analysis of many biological characteristics observed in human studies. By selectively breeding animals that exhibit distinct characteristics of alcoholism, researchers can explore the neurochemical differences between the animals serving as models for alcoholism and control animals. For example, rats that display a preference for drinking alcohol have been selectively bred to develop the alcohol-preferring (P) rat line. As control animals, rats exhibiting a strong aversion for alcohol have been bred selectively to produce the nonpreferring (NP) line. Neurochemical studies of these animals have revealed that P rats consistently have lower serotonin levels than NP rats in select regions of their brains. To date, a number of genetic animal models have been developed, providing knowledge of alcohol-seeking behavior as well as of neurochemical substrates of intoxication, dependence, and withdrawal.

Alcohol and the Cell Membrane

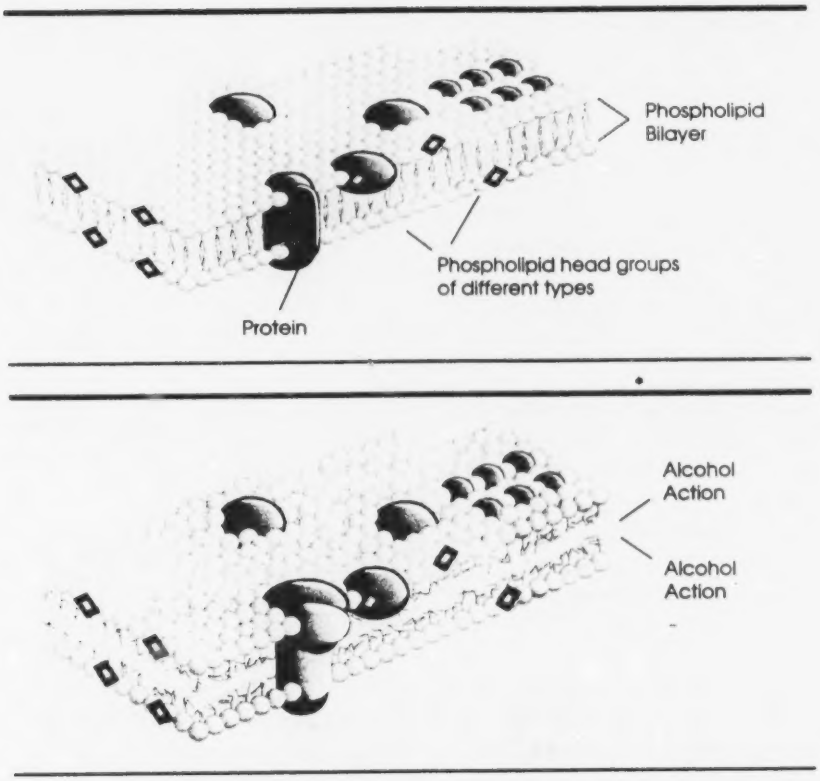
It has been suggested that the effects of alcohol may arise from its ability to disrupt the cell membrane: Alcohol has some ability to dissolve in water as well as in the fatty substances that comprise the cell membrane.

Regardless of the cell type, every cell has a membrane that provides a physical barrier between the inside and outside of the cell. The receptors discussed previously are embedded in the cell membrane. The cell membrane also serves additional functions. It gives the cell its shape and acts as a gatekeeper, allowing only selected molecules, such as water; certain nutrients; and selected ions to enter the cell. Alcohol molecules also may cross this barrier.

Changes in the chemistry of the cell membrane are an important topic in alcohol research. Cell membranes are composed primarily of lipids (fat or fat-like substances) and proteins. To varying degrees, alcohol can dissolve in the cell membrane and weaken the bond between lipid molecules in the membrane, causing the lipids to become disordered. Thus, alcohol may cause the membrane to lose some rigidity and become more fluid. Such fluidization may alter the function of proteins embedded in the membrane, thereby impairing the ability of nerve cells to process information.

Much of our knowledge of neurotransmitters and receptors has been attained through studies using genetic animal models of alcoholism.

Research has suggested that it is unlikely that changes on a broad scale in membrane fluidity can account for most of the effects of alcohol. Yet, a change in the physical properties of a particular "microdomain"—a membrane region that circumscribes an important functional protein such as a receptor or ion channel—could be part of the explanation of the effects of alcohol on brain function. Advanced techniques of physical chemistry and biophysics now permit this vital area of investigation to be pursued.



The nerve cell membrane is composed mainly of lipids arranged in a bilayer, within which are inserted various proteins, including receptors for neurotransmitters. Alcohol may distort the orderly arrangement of membrane lipids, thereby altering the function of membrane proteins. The top figure illustrates normal membrane lipids; the bottom figure illustrates membrane lipids distorted by alcohol. Courtesy of Dr. Boris Tabakoff.

Signal Transduction and Second Messengers

The binding of such chemical messengers as neurotransmitters or neuromodulators to a receptor elicits an effect in the receiving neuron. For example, the messenger may signal the neuron to fire, or it may direct the neuron to ignore firing signals from other receptors. In addition, the signal of the chemical messenger may trigger a metabolic event in the receiving neuron. The process of the conversion of a signal to a chemical or physiological action is known as signal transduction. Signal transduction involves specialized proteins (such as the G protein), as well as a family of enzymes involved in the generation of molecules, known as second messengers, that act to relay the message within the cell. Recent research indicates that alcohol's effect on second messenger systems may influence the biochemistry of neural transmission and signal transduction.

The membrane-bound enzyme, adenylate cyclase (AC), is linked to various neurotransmitter receptors and plays a role in synaptic transmission. Adenylate cyclase regulates levels of the second messenger cyclic AMP (cAMP) within the cell. cAMP affects protein activity and synthesis; thus, its proper functioning is important to long-term cellular consequences for cellular well-being. Three linked components—a receptor in the membrane, a regulatory protein known as the G protein, and a catalytic unit of AC—contribute to the expression of AC activity.

Some research findings suggest that the G receptor may be the site for alcohol's effects on this system. For example, in the brain striatum (an area believed to be important in motor and cognitive brain functions), the neurotransmitter dopamine appears to stimulate AC activity by interacting with G protein and the AC catalytic unit. Alcohol appears to enhance the effects of dopamine on AC activity, possibly by activating the G regulatory protein. In turn, AC activation increases cAMP levels in the cell. Researchers recently have shown, however, that brain cells adapt to long-term exposure to alcohol by reducing AC-stimulated cAMP levels: Cells begin to require alcohol to achieve normal levels of AC-stimulated cAMP. This process may represent a form of cellular "dependence" on alcohol. Because the AC system is common to several neurotransmitter systems, future studies of alcohol's effects on AC hold great promise for identifying the mechanisms that underlie these effects.

The effects of alcohol on second messenger systems can modify a neuron's electrical excitability and chemical properties. These systems, which play key roles in signal transduction, appear to be involved in many of alcohol's actions on the brain. Much of our knowledge about alcohol's effects on second messenger systems is preliminary yet promising—a foundation for exciting research advances in this area in the coming decade.

Alcohol and Neural Networks

The brain functions by analyzing and transmitting many pieces of

information simultaneously. Thousands of interconnecting neurons fire at the same moment, communicating a host of distinct messages within the brain. These interconnecting neurons may be thought of as the wiring for distinct nerve message tracks, known as neural networks. The brain must simultaneously process, integrate, and appropriately respond to all of the signals received from the many neural networks.

Although the actual process is likely to be exceedingly complex, a simplified model of the brain events that may transpire with alcohol use illustrates how simultaneous processing from distinct neural networks might affect brain function. As an individual drinks alcohol, the brain simultaneously processes details about alcohol's taste, smell, rewarding and anxiolytic effects, and caloric value and even about previous drinking experiences. In some individuals, genetic or other factors might cause networks involved in a specific activity, such as the communication of euphoria, to prevail over circuits that convey other information on the effects of alcohol, creating an inaccurate and inappropriate assessment of the physiological events that have transpired. Such imbalances in neural information processing could be a significant factor in fostering drinking, in craving, and in developing alcohol abuse and alcoholism.

During the next decade, our study of information processing will help us to identify the specific neural networks important in alcohol use and to determine their role in alcohol abuse and alcoholism. Innovative electrophysiological and computer technologies will enhance our efforts to define these networks, to record their physiological and electrical activity, and to experimentally manipulate multiple groups of neurons to learn more about their role in the brain. Further, we can use laboratory-generated information about simple systems to build models of circuits in the human brain.

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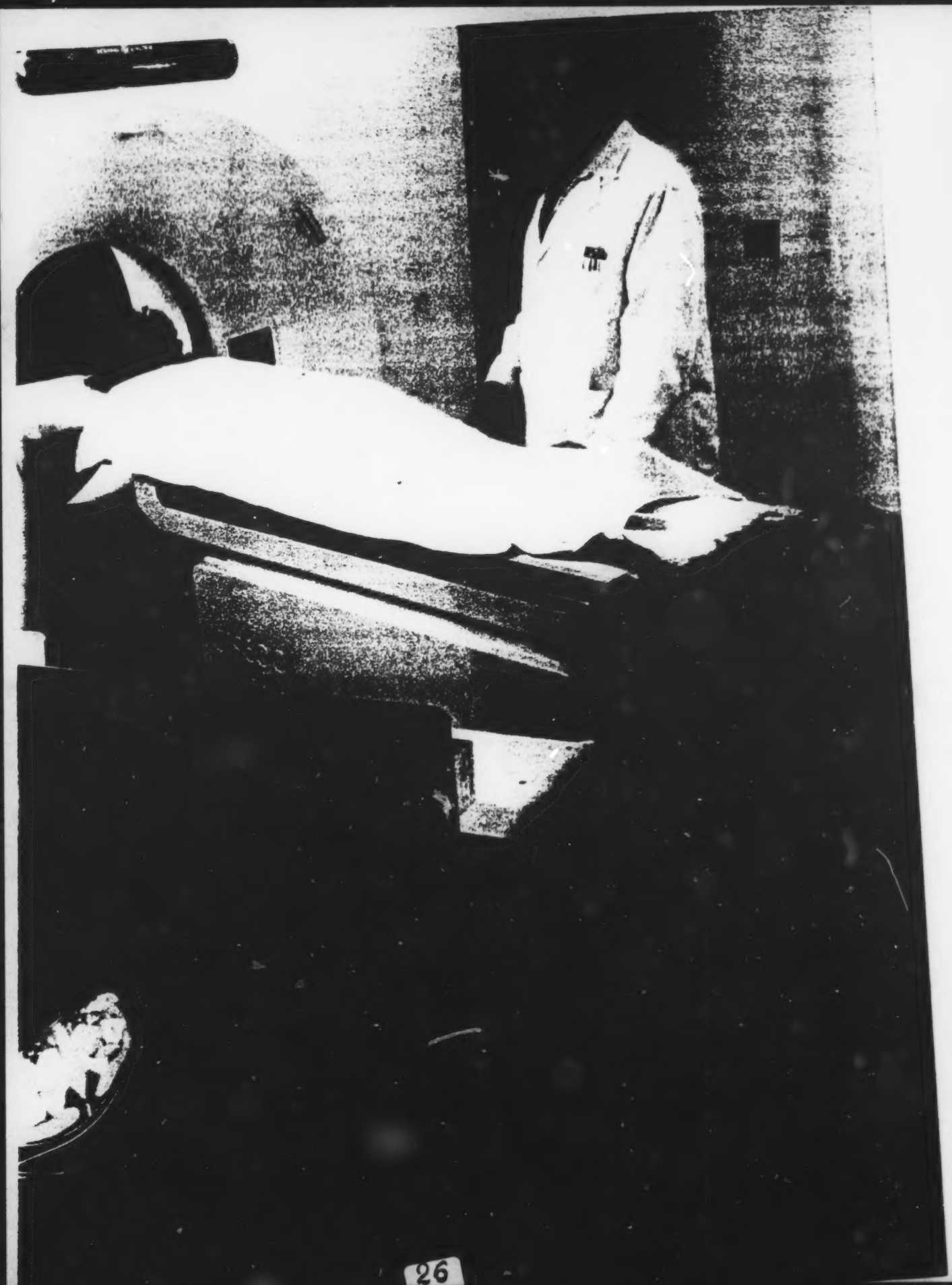


FOCUS ON BRAIN IMAGING TOOLS

The most important sites of alcohol's actions undoubtedly lie within the brain. It is the actions of alcohol on the brain that produce intoxication, reinforcement of continued alcohol use, and important features of the disease process of alcoholism.

Until recently, studies of alcohol's actions on the brain could be conducted only after a patient's death, when the brain could be examined physically. Although autopsy studies permitted scientists to examine the brain lesions and cell loss that can result from heavy drinking, these investigations provided little knowledge about alcohol's interaction with the biochemical pathways in the living brain that produce intoxication, craving, dependence, and tolerance. Moreover, researchers were unable to examine the events in the living brain that place some individuals at greater vulnerability than others to alcoholism.

With the development of noninvasive imaging techniques, researchers have the exciting opportunity to explore inside the living brain and probe its biochemistry and physiology. No longer restricted to autopsy studies, alcohol researchers now can use imaging tools to follow alcohol-induced changes over time in the brains of living people and to relate these changes to thinking and behavior.

By providing an altogether new approach to assessing alcoholism, imaging techniques offer new promise in the quest for answers to such fundamental questions as:

- Do chemical changes in the brain produce such features of alcoholism as craving for alcohol and impaired control over drinking behavior? What region(s) or biochemical pathway(s) in the brain are involved in these processes?

The MRI scanner uses magnetic fields and radiofrequency waves to form exquisitely detailed three-dimensional pictures of anatomical structures in the body. Photograph courtesy of Dr. Adolph Pfefferbaum.

- How does chronic alcohol abuse damage brain tissue? Are some regions of the brain more sensitive than others to the deleterious effects of alcohol? Are some individuals more vulnerable to this damage than others? Does abstinence reverse the damage? Is there a predictable relationship between the physical damage to the brain and the loss of certain mental capabilities experienced by some alcoholics?

- Recognizing that genetic factors contribute to the risk of developing alcoholism, are there inherent differences in the central nervous system that differentiate persons at higher risk and lower risk for alcohol addiction? Do high-risk individuals respond differently to alcohol than low-risk individuals? Is the vulnerability among high-risk individuals specific to alcohol or do these individuals respond similarly to other drugs of abuse? Are early signs of withdrawal or physical dependence more apparent in high-risk individuals than in low-risk individuals after administration of alcohol? Which neural systems are involved?

Currently, a variety of imaging tools are available to researchers and clinicians. Some methods provide information about the size, shape, and physical integrity of the brain. Other approaches assess the brain at work by measuring electrical activity, blood flow, oxygen and glucose use, and neurotransmitter activity. Although each technique has distinctive strengths, the coupling of two or more approaches can provide multifaceted knowledge about the brain structures and functions involved in the vulnerability to and expression of alcoholism. Some of these new techniques are described in the sections that follow.

Imaging Techniques

Positron Emission Tomography

Positron emission tomography (PET) is one of the most powerful of the new noninvasive scanning technologies. This technique employs short-lived radioisotopes, linked to a key molecule such as sugar or oxygen, which are introduced into the body. As the compounds enter the brain, they emit radioactive energy (a positron) that is detected by special cameras arranged around an individual's head. With the aid of a computer, the emitted radioactivity is processed into a three-dimensional image of the brain that shows the distribution and concentration of the radioactive compounds.

PET offers an exciting opportunity to view directly the brain networks and physiological and biochemical processes involved in specific behaviors or functions. For example, PET can map brain activity by tracking and measuring brain glucose metabolism. Glucose is the sole source of energy for the brain. Thus, systems of the brain involved in various functions or tasks metabolize glucose to obtain energy to perform work. By using PET to trace the distribution of radiolabeled glucose throughout the brain, scientists can identify those systems and regions involved in a specific behavior or function. PET also can detect changes in glucose levels in localized brain regions, thereby revealing systems that use more energy than others. In this way, researchers can identify systems that become more active than others as an individual exhibits a behavior or performs a task.

In addition, PET can be used to examine specific brain neurotransmitter systems. To date, tracers developed for the study of dopamine and serotonin neuroreceptors have

This color-coded, three-dimensional PET image of the brain, constructed from 16 two-dimensional brain slices, depicts glucose utilization and thus, functional activity, in different brain areas. Orange, yellow, green, and blue correspond to a range of activity levels, with orange representing the highest level and blue the lowest level. Courtesy of Dr. Michael Eckardt.

enabled researchers to observe the binding of neurochemicals to receptors in living persons. Such studies hold great promise for identifying the role of various neurotransmitter systems in specific functions or behaviors.

Single Photon Emission Computed Tomography

Like PET, single photon emission tomography (SPECT) uses short-lived radioisotopes to follow metabolic activity and neurotransmitter system functioning. Unlike PET, however, SPECT uses injected radioisotopes that emit a gamma particle, producing a single photon that is recorded with a SPECT camera. Recent improvements in SPECT instrumentation make it possible to rotate the cameras in different planes. This technique, which can be employed to observe blood flow in the brain (to mirror closely brain metabolism), currently is enjoying widespread clinical application.

Magnetic Resonance Techniques

Magnetic resonance imaging (MRI) is a new structural imaging technique that provides exquisitely detailed pictures of the anatomical structure of any organ of the body, including the brain. This technique does not use ionizing radiation, such as x-rays. Rather, an individual, lying inside a large superconducting magnet, is exposed to magnetic fields. Exposure to magnetic fields and radiofrequency waves causes certain atoms in the brain to emit signals as the atoms align and realign within a field. The signals vary in intensity, depending on the substance from which they originate. MRI scanners use the signals emitted from atoms with odd numbers of protons, such as hydrogen (the most abundant element in tissue), to form three-dimensional images in which different types of tissue can be differentiated and specific anatomical structures of the brain can be outlined.

Computer-colorized magnetic resonance images of the brain from a healthy 57-year-old man and a 57-year-old man with a history of heavy alcohol consumption. Magnetic resonance images reveal detailed structural information, such as the neuroanatomical changes produced by alcohol. These changes are evident in the enlarged ventricles in the alcoholic's brain compared to the control's brain. Courtesy of Dr. Adolph Pfefferbaum.

This technique offers several advantages over other structural imaging devices. MRI produces images with amazing clarity using magnetic fields—not x-rays. Hence, an individual can have repeated MRIs without the risk of exposure to ionizing radiation. MRI also offers great flexibility for viewing the brain from many different directions. Finally, MRI allows scientists and clinicians to distinguish gray matter (primarily composed of nerve cells) from white matter (primarily composed of the long "wires," or axons, connecting nerve cells) within the brain.

Advances in magnetic resonance technology have broadened the application of this technology to allow the study of structure and of biochemistry of the living brain. Magnetic resonance spectroscopy (MRS), a new technique resulting from technological advances, uses the MRI scanner to examine the proton signals of molecules such as fat, amino acids (the building blocks of proteins), and metabolic products, which behave differently in a strong magnetic field. The resulting images provide detailed

information about the metabolic state of regions of brain tissue. MRS also may measure magnetic resonance signals from phosphorus atoms, thus providing information about the concentrations of compounds critical to cellular energy. The concentrations of these compounds correspond to the activity of the specific systems or networks in the brain.

Until recently, the use of MRS was limited to assessing the chemical composition of a single volume of material without constructing an image. With new technological advances, however, it is possible to produce three-dimensional images that detail the chemical events occurring within the organ under study. Currently, MRS produces images of coarser resolution than those of PET. Yet, as MRS technology improves, it will offer researchers a unique opportunity: Because, unlike PET, MRS does not use radiolabeled tracers, MRS can be used repeatedly on the same individual, allowing researchers to examine specific metabolic and physiologic events over time.

Electroencephalography

The electroencephalogram (EEG), measured with electrodes placed in standard positions on the scalp, is a record of the spontaneous electrical activity within the living brain. The normal human EEG usually is classified into four major brain waves: beta, alpha, theta, and delta. Each wave has a distinctive amplitude and frequency. Characteristic wave patterns occur in varying proportions with different behavioral states. For example, as a person passes into sleep, the slower frequency delta wave becomes predominant. These changes in frequency can be quantified with computer techniques.

EEG also reveals the effects of drugs, metabolic conditions, and injury (such as head trauma and stroke) on brain electrical activity. Such factors can produce abnormal patterns, reduced wave amplitude, and a shift in wave frequency.

Event-related potential (ERP), a technologically advanced EEG method, measures specific electrical responses to a sensory stimulus, such as a sight or a sound. EEG electrodes are placed on the scalp to measure the electrical responses within a fraction of the second that follows the delivery of the external stimulus. The ERP waveforms, which result from the activity of the various brain processes that occur in response to outside stimuli or endogenous brain activity, are embedded in background EEG noise. Thus, a computerized method, known as averaging, must be used to extract the characteristic waveforms of the evoked responses from the background EEG activity. The ERP technique has the unique value of measuring mental activity that occurs on the order of milliseconds, providing an immediate record of brain activity associated with sensory and cognitive processing.

Today's imaging technology will enable researchers to observe directly the dynamic mechanisms that are the disease of alcoholism.

Recent advances in computer technology and mathematical analyses of signals have made it possible to assess the spatial and temporal properties of event-related brain potentials. One such method, known as dipole source localization, has as its basis the dipole, the simplest current source in the brain. With dipole source localization, the ERP is modeled as arising from multiple intracranial electrical dipole sources. This method offers great promise as a means to partition ERP waveforms emanating from concurrently active brain regions into subprocesses that are anatomically localized as biophysical sources of electrical activity.

Imaging Techniques in Alcohol Research

Heretofore, alcohol researchers have attempted to understand alcoholism by examining the external manifestations of the disease. Today's imaging technology will enable researchers to observe directly the dynamic mechanisms that are the disease.

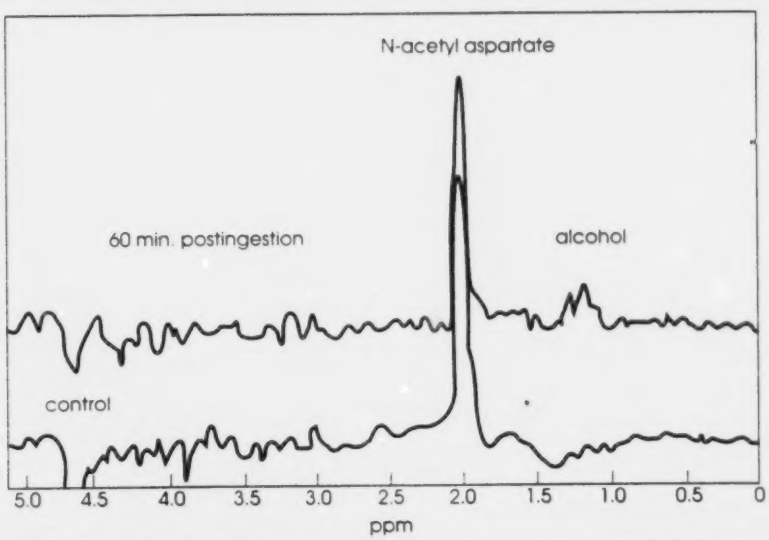
Each of the imaging tools discussed, with its distinctive strengths, can provide key information about structural and functional brain injury associated with alcohol use, about vulnerability to alcoholism, and about the brain processes and anatomical sites involved in elements of the disease (craving, impaired control, dependence, tolerance, and relapse and recovery). Collectively, this information can provide a complete picture of the disease process.

Any consumption of alcohol appears to affect numerous metabolic, physiologic, and neurotransmitter systems in the brain. Additional research is needed to identify the systems involved, to determine how they are affected, and to understand how alcohol's actions on one system may influence other systems in the brain. Imaging techniques can be vital to this research. Specifically, PET, SPECT, and MRS have the potential to trace the regional brain distribution of alcohol and to characterize alcohol's effects on the biochemistry and physiology of these various brain regions. Because MRS does not expose people

to radioisotopes, it offers the distinct opportunity to examine the same study subjects repeatedly and follow alcohol's actions in the brain over time. Superimposing MRI images over all of these maps of brain function will help to identify the brain structures affected by alcohol's actions. In addition, ERP mapping studies can show alcohol's effects on electrical activity within various brain regions. When considered together, these findings will enable researchers to study the effects of alcohol on specific brain systems and structures, potentially providing insight into how drinking alcohol can produce pleasurable sensations, reduce anxiety, alter mood, influence cognitive processing, and cause sedation.

Efforts to identify why some people seemingly possess a greater vulnerability for developing alcoholism than others may be facilitated greatly with imaging techniques. Already, electroencephalography studies have provided fascinating information in this regard. Alcohol appears to affect EEG activity in high-risk persons differently than in low-risk individuals: After drinking, greater variations in fast EEG activity are observed among high-risk sons of alcoholic fathers than among low-risk individuals. Using ERP, researchers have found that alcohol-naive sons of alcoholics display reduced amplitude of the P3 wave, a genetically determined wave that appears during the performance of cognitive tasks. This trait may be a marker for genetic vulnerability. These early findings suggest that electroencephalography will provide much knowledge about the function of electrical activity in genetic susceptibility to alcoholism.

Electroencephalography studies no doubt will continue to broaden our knowledge of the genetic factors involved in the development of alcoholism; yet, other imaging approaches also can contribute significantly to this understanding. Using MRS, PET, and SPECT, scientists can address a critical question concerning the role of functional processes in susceptibility to alcoholism: Are there inherent functional differences in some individuals that cause them to respond to alcohol differently than others? Imaging techniques may reveal that some individuals respond differently to alcohol because it may affect different systems in them than it does in others. With



Using magnetic resonance spectroscopy, alcohol, which produces a spectrum different from those of water and lipid, can be detected in the human brain. This spectrum illustrates an alcohol signal from a localized brain region, following consumption of wine. Adapted from Pfefferbaum et al. Proceedings, Annual Meeting of College of Neuropsychopharmacology, December 1990.

these techniques, researchers can gain new insight into the role of certain functional processes in producing heritable vulnerability to alcoholism.

Specific states and behaviors of alcoholism, such as relapse, may be linked to physiologic processes in the brain. Imaging tools can help researchers to identify and more fully understand these brain processes. For example, behavioral changes often are observed in recovering individuals prior to a relapse to drinking, suggesting that a physiological event in the brain may account for the observed change in behavior. Until now, scientists have not had the means to search for and identify the brain processes that underlie relapse. Noninvasive imaging technology provides a window through which scientists can study the biochemistry and physiology of the living brain. By using PET and MRS to examine brain biochemistry and physiology before, during, and after relapse, scientists well may define the neural processes involved in the return to drinking. This knowledge, in turn, should lead to recognition of the means by which the brain processes underlying relapse may be controlled—greatly enhancing the potential for recovery.

Imaging tools also provide great opportunity to examine the injury to brain structures and processes that results from chronic drinking. MRI studies have shown that the percentage of gray brain matter declines with age, while the percentage of white matter remains relatively constant. Alcoholics, however, have significantly less gray and white brain matter than their nonalcoholic peers, suggesting that alcohol may accelerate the brain's aging process.

Future studies using MRS, PET, SPECT, and ERP will enhance our understanding of this process, possibly characterizing functional disturbances associated with chronic drinking. Chronic drinking can impair a person's ability to reason and to process information. These tools will enable researchers to identify the underlying brain injury that produces this impairment. Further, imaging tools will allow scientists to examine whether abstinence leads to reversal of the damage.

Similarly, these tools will enhance greatly our knowledge of alcohol's injurious effects on the developing brain. Children born to alcohol-abusing mothers may exhibit a number of characteristic alcohol-related defects, classified clinically as fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Damage to the central nervous system is one of the most profound defects in FAS and FAE

Patterns of electrical activities, marked by the color shading, are different in individuals who are at risk for developing alcoholism (top) than in low-risk individuals (bottom). Courtesy of Dr. Henri Begleiter.

children, resulting in neurologic abnormalities, developmental delays, behavioral problems, and intellectual deficits. A significant need exists to correlate the behavioral and intellectual dysfunctions seen in the children with underlying brain abnormalities. The use of noninvasive functional and structural techniques allows for detailed study of brain anatomy and activity in these children. Coupling these tools with tests to assess neuropsychological problems in children will allow researchers to identify the extent and nature of fetal alcohol effects in individual children. These technologies also may pinpoint the specific brain areas that appear most vulnerable to alcohol's actions during development. In addition, noninvasive imaging tools can help to classify the severity of alcohol-related brain injury.

Finally, imaging tools will enable researchers to follow the effects of treatment by observing the changes that may occur within the brain, not only as a result of medications but also as individuals experience traditional behavioral and verbal therapies. Although traditional therapy approaches benefit a large number of alcoholics trying to achieve and maintain sobriety, it remains to be determined how these approaches influence recovering individuals. The effect of successful therapy on brain processes and cognitive behavior of patients currently cannot be studied. Imaging tools—especially ERP, PET, and MRS—eventually may provide a means to observe adaptations in neural systems that occur over time in response to successful therapy. Moreover, such studies can provide insight into understanding why various treatment approaches are ineffective for some alcoholics and may help to distinguish the forms of treatment most suited to particular patients. Ultimately, these studies may provide useful information for defining subtypes of alcoholics.

Imaging technologies also can contribute significantly to research on development of new medications for alcoholism treatment. Although the potential for pharmacological treatment is widely recognized, few medications are available today. However, imaging tools will enable researchers to observe the actions of potential medications on specific neural systems and to test their efficacy in mitigating alcohol problems.

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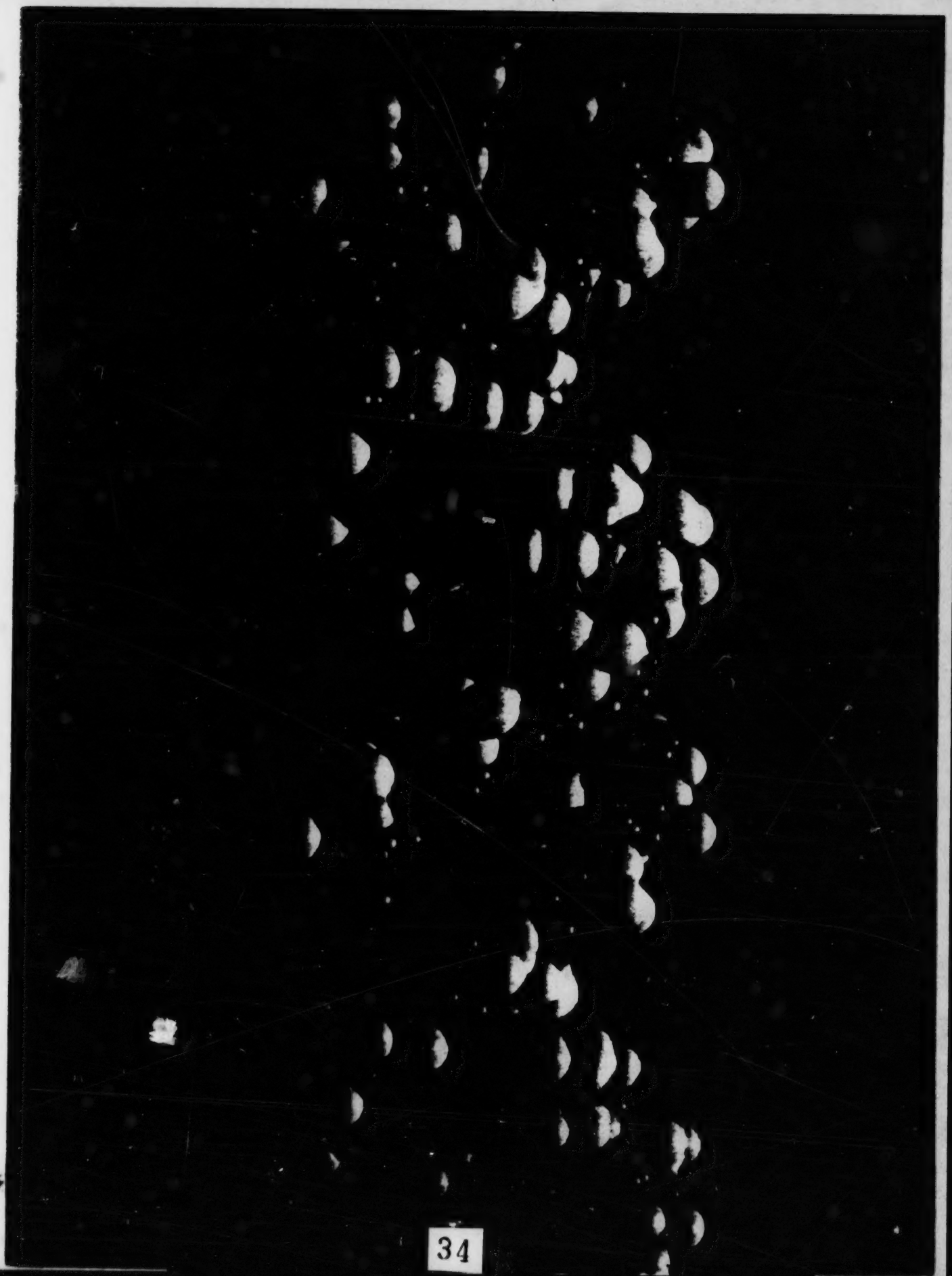


III GENETICS AND ENVIRONMENT

People vary considerably in their drinking behavior and in their sensitivity to alcohol's effects. Some individuals drink only moderate amounts of alcohol and experience few, if any, problems from their drinking. Others, however, become addicted to alcohol and may develop serious medical consequences, encounter adverse social difficulties, or experience both as a result.

The vulnerability that some people seemingly possess to developing alcoholism has prompted researchers to search for factors that may contribute to heightened susceptibility. The legacy of alcoholism in families and among certain ethnic groups suggests that genetic factors can increase an individual's vulnerability for this disease. On the other hand, researchers also have observed that individuals within certain ethnic groups have protective genetic factors that make it doubtful they will ever abuse alcohol.

Nevertheless, the distribution of alcoholism within any given population indicates that genetic factors alone cannot account for the development of the disease; environmental factors also have an important effect on drinking. Family dynamics, peer influences, cultural values, everyday stresses, and a host of other influences shape our thinking about alcohol and affect our drinking behavior.

In an attempt to understand why only some people who drink advance to problematic drinking, alcohol researchers are exploring the age-old question of nature versus nurture. This research, to date, has yielded a wealth of knowledge about the genetic determinants of alcoholism—knowledge that has led to profound changes in society's view of alcohol abuse and alcoholism as matters of public health.

The modern public health model of disease holds that many human illnesses

Computer drawn deoxyribonucleic acid (DNA) illustrates the double-stranded helical conformation of this important molecule. Outside strands are composed of deoxyribose sugar and phosphate; linked pairs of bases that connect the strands of the helix determine genetic coding. Courtesy of NIH archives.

result from the interaction of environmental and genetic factors. The susceptibility to high cholesterol levels is an example of this model: Although genetic makeup may heighten an individual's risk for high blood cholesterol levels, regular exercise and a diet low in saturated fat and cholesterol could counteract much of this genetic vulnerability. The awareness that alcohol-related problems follow this same gene-environment model has influenced greatly the course of alcohol research during the past decade.

In addition, the results of several pivotal adoption and twin studies conducted over the past 25 years suggest that alcoholism is a heterogeneous disorder, with some forms that are highly heritable and others that are less so. Alcoholism, like hypertension, coronary artery disease, and diabetes, appears to be a disorder in which environmental factors activate genetic components. In other words, genetic predisposition does not imply predestination: Environmental factors are needed for alcoholism to develop in persons who have inherited a vulnerability for the disease.

Although much remains to be learned about the specific biological factors involved in the development of alcoholism, it now is recognized that alcoholism stems from a complex interplay between genetic and environmental factors. This knowledge opens avenues for developing medications and other biological therapies that compensate for genetic susceptibility. Moreover, it lays the foundation for conceiving prevention, early intervention, and treatment methods that focus on changing environmental risk factors for alcohol abuse and dependence. For example, neuropharmacologists one day may develop a medication that can counterbalance a genetic factor that enhances nerve cells' vulnerability to the effects of alcohol. At the same time, behavioral researchers may devise psychotherapeutic techniques to help genetically vulnerable individuals deal more effectively with drinking-related stressors and craving.

However, little is known about the way that genes and environment interact to produce different types of alcohol-related problems. Researchers acknowledge that such factors as personality, cognition, and sociocultural norms contribute profoundly to the development of alcohol abuse and alcoholism. In the next decade, studies focusing on gene-environment interplay will provide insight into the genetic mechanisms involved in the development of alcoholism.

It is now recognized that alcoholism stems from a complex interplay between genetic and environmental factors.

Genetic Sources of Vulnerability

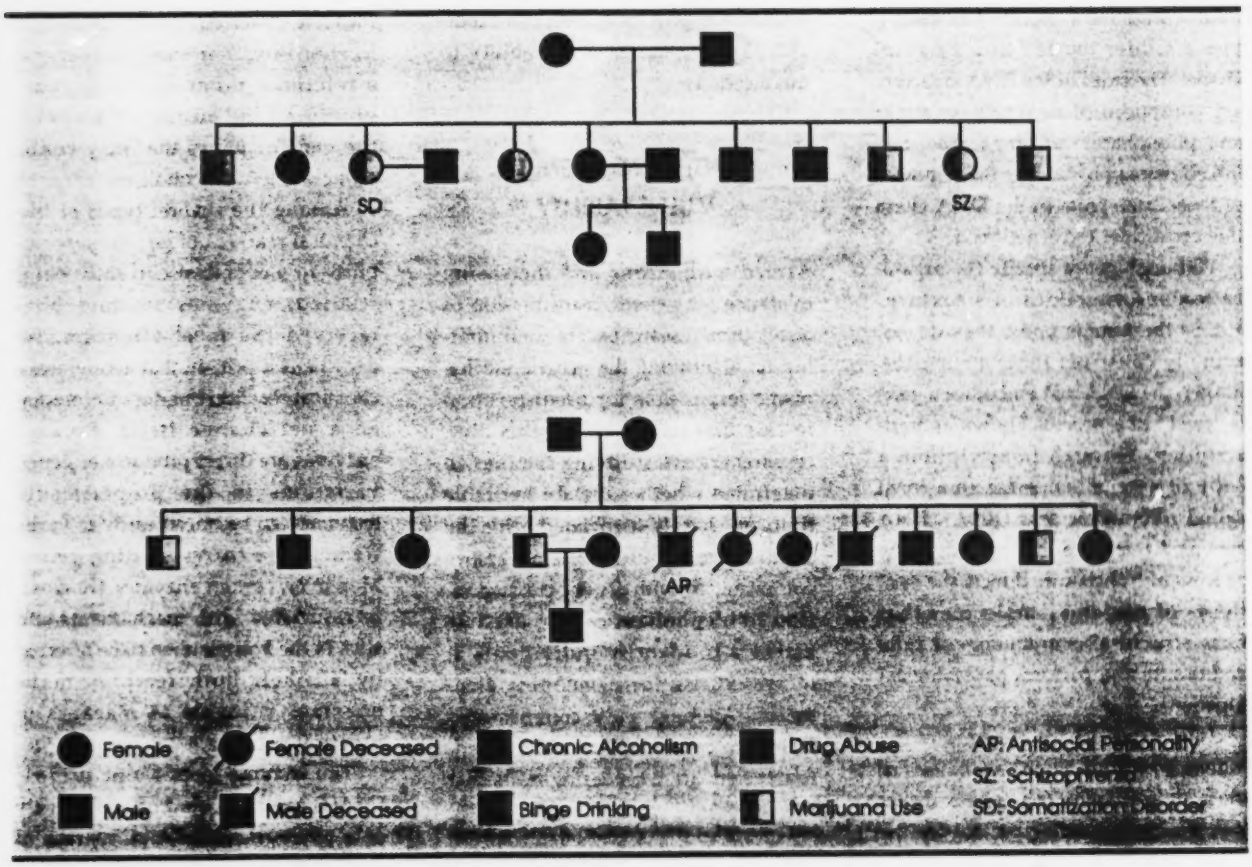
Studies of persons raised in adoptive homes from an early age provided the earliest clues that genetic factors play a role in alcoholism and that environmental factors influence whether a person with genetic vulnerability for alcoholism actually develops the disease. Adoption studies help to untangle the contributions of genes and family environment, allowing these elements to be evaluated independently. The effects of genetic factors can be estimated by comparing individuals with different genetic backgrounds who are raised in the same home (such as adoptees and their nongenetic siblings); environmental influences can be assessed by comparing genetically related individuals (such as adoptees and their nonadopted genetic siblings) who are raised in different environments.

An adoption study in Denmark revealed that the adopted-away sons of alcoholics were more than three times as likely to become alcoholic as the adopted sons of nonalcoholics. A large-scale study in Sweden confirmed these results, showing that the incidence of alcoholism among male adoptees born to severely alcoholic fathers was three-and-one-half times greater than among adopted sons of nonalcoholic men. In addition, male adoptees of alcohol-abusing biological mothers were almost twice as likely to become alcohol abusers themselves as male adoptees born to mothers who did not abuse alcohol.

Analysis of the Swedish adoption studies revealed the existence of two prototypic forms of alcoholism that differ in inheritance patterns, alcohol-related behaviors, personality traits, and environmental influences. Type I alcoholism, also known as milieu-limited alcoholism, is a more common form that occurs in both men and women and is associated with adult-onset alcohol abuse in either biological parent. This form is called milieu-limited because its expression requires both genetic predisposition and environmental provocation.

Type II alcoholism, also known as male-limited alcoholism, is a severe type of predisposition found only in men. Less common than Type I, Type II is associated with severe, early-onset alcoholism in the biological father. Its transmission is highly genetic and appears to be unaffected by environment.

As with other genetically transmitted diseases, the search for genetic factors responsible for susceptibility



Studying family pedigrees enables researchers to assess familial frequency of alcoholism. Courtesy of Dr. David Goldman.

to alcoholism has involved several stages. Studies in the primary stage involved a close observation of familial incidence. In the next phase, studies focused on analyzing families to determine whether environment or genes caused the family linkage. At present, genetic research on alcoholism is moving into the area of molecular biology to isolate and identify the gene or genes that may confer vulnerability for this disease.

Molecular Biology: Studying the Chemistry of Inheritance

Molecular biology is a relatively new area of science in which knowledge of normal physiology and of disease is gained through the study of genes. Located in the nucleus of the cell, genes carry information for hereditary characteristics. Housed within genes are complex sets of instructions that direct the development, organization, and functioning of the human body. The scores of instructions are contained not in one gene but, rather, are found in thousands of genes. Genes are organized and stored in structures known as chromosomes, each of which contains thousands of genes.

By their chemical structure, genes control every detail about development of the body: They specify the body's size, shape, and color and provide directions for the functioning of bodily systems, such as the nervous and circulatory systems. Genetic information is coded in the deoxyribonucleic acid (DNA) molecule, the primary component of genes. DNA is a giant

double-stranded molecule that resembles a ladder twisted into a helical shape. The sides of the DNA structure are composed of deoxyribose sugar and phosphate; the rungs consist of linked pairs of bases. It is the sequence of these base pairs in the DNA chain that constitutes the genetic code.

Although genes specify the organization and functions of structures within the human body, they do not actually construct these structures. Rather, the DNA that embodies a gene is "read" in a process known as transcription. Through transcription, a copy of a gene is created in a form called ribonucleic acid (RNA). RNA acts as a template and, through the process of translation, directs the synthesis of proteins—molecules that form structural components of cells and tissues and perform physiological functions.

Thus, genes are the blueprint of the human body, directing the synthesis of the body's proteins. If a gene is defective, the corresponding protein will be defective, resulting in a structural or functional abnormality. Such abnormalities are the basis of genetic diseases.

The tools of molecular biology enable researchers to study the connection between genes and corresponding proteins. Various techniques can be used to isolate specific DNA fragments for study. Numerous copies of a gene subsequently can be reproduced with a technique known as molecular cloning. Additional techniques permit researchers to read the sequences of the base pairs in the DNA fragment that comprises the gene. By so doing, they can determine whether a change in the base sequence accounts for a particular genetic defect.

In alcohol research, molecular biology has revolutionized the search for genetic determinants of alcoholism. By applying molecular cloning techniques, researchers now have tools that potentially can identify and characterize the genes involved in an individual's heightened vulnerability to this alcoholism.

Identifying Genetic Vulnerability

Armed with strong and increasing evidence for genetic transmission of alcoholism, researchers are concentrating on identifying the genetic mechanisms responsible for predisposition to this disease. Towards this aim, researchers are studying families to determine whether certain heritable traits are highly associated with the occurrence of alcoholism. Traits cotransmitted with genetic predisposition to alcoholism can be used as markers to identify individuals at increased risk for developing alcoholism. Although these cotransmitted traits have not yet been identified, researchers are considering traits that may be linked to genetic susceptibility to alcoholism within three promising categories: Behavioral traits (impulsive and violent behavior), physiological traits (EEG abnormalities, upper body sway), and biochemical traits (enzymes involved in neurotransmitter metabolism). Once the associated markers are identified, the genes that produce them can be located, isolated, and cloned. The location of such markers can serve as a reference point on the genome, providing the means for mapping the gene or genes that may confer vulnerability to alcoholism.

Adenylate cyclase is another enzyme that is receiving considerable research attention as a possible marker of predisposition to alcoholism.

Among the several types of biochemical markers of genetic susceptibility to alcoholism currently being studied, enzymes to date have received the most attention. An enzyme is a protein that accelerates a chemical reaction but does not undergo a net change itself. Because enzymes are direct products of genes, variations in the properties of enzymes can be traced easily to variations in the corresponding genes. Moreover, certain enzymes are closely associated with mechanisms and sites in the body known to be affected by alcohol. Both features make enzymes valuable as markers of genetic involvement.

The enzyme monoamine oxidase (MAO) has been studied extensively as a potential biochemical marker of predisposition to alcoholism. Monoamine oxidase is involved in the metabolism of several neurotransmitters implicated in certain aspects of alcoholism. Several studies have reported abnormally low MAO levels in blood platelets of alcoholics compared with those of nonalcoholics. Moreover, because genetic factors control variations in MAO levels among people, researchers believe that this trait is not a secondary effect of alcoholism. Recently, investigators have associated low levels of platelet MAO with the highly heritable Type II alcoholism but not with the more environmentally influenced Type I. This finding demonstrates that biochemical differences are likely to exist between the two subtypes of alcoholism.

Adenylate cyclase (AC) is another enzyme that is receiving considerable research attention as a possible marker of predisposition to alcoholism.

Found in the central nervous system, this enzyme is involved in the formation of second messengers—intracellular chemicals that perform biochemical functions that ultimately result in a physiological or a behavioral response. Adenylate cyclase activity can be stimulated experimentally by numerous substances, including the salt cesium fluoride and the hormone prostaglandin E_1. However, AC stimulation by either of these agents appears to be significantly lower in alcoholics than in nonalcoholics. The persistence of this effect in alcoholics suggests that it may be a marker of genetic risk for alcoholism, an interesting possibility currently being investigated.

Genetics researchers also are pursuing research aimed at identifying electrophysiological markers of inherited predisposition. Communication within the brain involves bioelectric impulses that begin in response to chemical signals. One brain electrical phenomenon that appears to be a strong indicator of genetic vulnerability to alcoholism is the P3 signal, a brain wave that normally appears during the performance of various cognitive or learning tasks. This wave repeatedly has been shown to be weaker in young boys who have never drunk alcohol but are at risk of alcoholism because their fathers were alcoholic. Early studies had found the same reduced P3 wave amplitude in adult alcoholics who had become abstinent, raising the possibility that the reduced amplitude may be a consequence of and not an antecedent to alcoholism. However, the discovery that reduced P3 amplitude is present in alcoholism-susceptible boys who have never consumed alcohol indicates that it precedes the development of alcoholism and is a potential genetic marker of susceptibility.

Heritable characteristics that may be associated with alcoholism can serve as "sign posts" that point to the general location of the genes responsible for the development of alcoholism. Although the characteristics themselves may not be responsible for the development of alcoholism, they represent identifiable factors that can be associated with alcoholics. For example, if three characteristic markers are always identified with alcoholism, these markers are said to be linked to the development of alcoholism. Such linkage suggests that the genes for the markers lie on the same chromosome and are in close proximity to the gene or genes responsible for alcoholism.

Using molecular biology techniques, researchers can determine the position of these markers on the human genome. It is anticipated that a sufficient number of markers will be identified within the next few years to allow researchers to produce highly resolved genetic maps. Genetic maps label the position of known genes (markers) on a chromosome. As the locations of more and more markers are determined, the map becomes highly resolved. High-resolution genetic maps will enable researchers to detect, through linkage analysis with marker genes, those genes responsible for susceptibility to alcoholism. Identifying these genes is an important long-term goal in the study of the human genetics of alcoholism—a goal that eventually can lead to a systemic approach to preventing and treating alcoholism.

Through a large collaborative study, presently ongoing at six sites across the United States, scientists have embarked upon a systematic effort to identify the gene or genes responsible for predisposition to alcoholism. Scientists will study large families of alcoholics by methodically collecting biological material and by conducting neuropsychological and personality assessments. This multidisciplinary, multisite project is

expected to lay the groundwork for future genetic research on alcoholism by yielding fundamental knowledge about possible biological markers and genetic, psychological, and environmental risk factors associated with susceptibility to developing alcoholism.

Genetic research on alcoholism is not limited to identifying and characterizing traits associated with increased vulnerability. Rather, researchers also are interested in defining the factors that appear to protect certain people from pathologic drinking, thereby protecting them from the development of alcoholism. A notable and extensively studied protective phenomenon is the flushing reaction to alcohol observed in many people of Asian heritage. The flushing reaction—manifested as a reddening of the face and upper chest as a result of vasodilation—produces such unpleasant symptoms as hot skin, increased heart rate, and lightheadedness. This response to alcohol long has been considered a deterrent to alcohol consumption, and scientists have hypothesized that the flushing reaction may account for reduced alcohol consumption and lower incidence of alcoholism observed in the Asian population compared to many other ethnic groups.

Molecular biology techniques were instrumental in identifying the biological factors that underlie the flushing reaction. Using these techniques, researchers showed that the inheritance of an abnormal gene for the enzyme aldehyde dehydrogenase (ALDH) was primarily responsible for producing the flushing reaction to alcohol consumption. ALDH is one of two enzymes involved in normal metabolism of alcohol. The variant form of ALDH produced from this abnormal gene is inactive, thereby preventing normal metabolism of alcohol. When individuals with this variant enzyme consume alcohol, the noxious alcohol metabolite acetaldehyde increases in their systems, leading to the flushing reaction. Studies in Chinese and Japanese persons have shown that the mutant gene occurs five times less frequently in alcoholic patients than in the general population. This finding is important because the frequency of this abnormal gene in the population may help to predict susceptibility to alcohol abuse.

In contrast to most Asian populations, Taiwanese aborigines have a high incidence of alcoholism. Scientists have shown that, unlike most Asians, members (85-90 percent) of the aboriginal group possess a normal gene for ALDH. Thus, the absence of the abnormal ALDH gene may be a contributing factor to the high rate of alcoholism among Taiwanese aborigines.

Abnormal genes found in other ethnic groups also may affect drinking behavior and contribute to alcohol abuse in these populations. For example, scientists have discovered that three variant forms (isoenzymes) of alcohol dehydrogenase (ADH)—identified as beta 1, beta 2, and beta 3—are found predominantly in white, Asian, and African-American populations, respectively. Because alcohol dehydrogenase (ADH) is the first enzyme involved in metabolism of alcohol, differences in the properties of this enzyme could affect the rate at which alcohol is metabolized in the body. Experimental studies have demonstrated that the isoenzymes metabolize alcohol at different rates, and researchers are beginning to determine the relevance of this finding to drinking behavior and complications of alcohol abuse.

The disparate distribution of these enzymes in Asian alcoholics compared to Asian nonalcoholics supports the belief that alcoholism may have a genetic basis in some persons. However, because many Asians who experience the flushing reaction continue to drink, it appears that the presence of various isoenzymes is only one of the many genetic factors that influence drinking behavior. Furthermore, environmental factors that influence alcohol consumption may alter or override the effect of these genetic factors on drinking behavior. In fact, recent studies have reported that alcohol consumption is increasing among Asians as a result of social pressure to consume alcohol. In addition, the nature of the specific ADH and ALDH genes in some individuals may produce a less severe aversive reaction that is less likely to serve as a deterrent in the presence of new cultural and social pressures. This new information suggests that future studies will require close observation of both the biological and psychosocial factors that influence drinking behavior.

Animal Models in Genetic Research

Animal models are an important tool in the study of genetic susceptibility to alcoholism because these models enable scientists to control for various biological characteristics observed in humans. Use of these models in experimental studies enables researchers to analyze potential genetic determinants of alcoholism. The findings gathered through animal research on alcohol, in turn, can be applied to the study of alcoholism in humans.

Most experimental animals avoid drinking alcohol under normal conditions. Thus, to develop an animal model that parallels the human disease, researchers have been faced with finding animals who actively will seek alcohol. This problem was resolved with the development of selectively

bred animal lines that differ greatly in their preference for alcohol. The diversity of alcohol preference in such animals provided evidence that this characteristic may be genetically influenced and suggested that animals may be bred selectively for this attribute.

As the next step in developing animal models for alcoholism, scientists had to resolve whether alcohol-preferring animals drink alcohol for its nutritional or caloric value, or for its pharmacological effects. Studies with rats bred selectively for alcohol preference demonstrated that these animals not only will work to obtain alcohol—pressing a bar more than 1,000 times a day—but also will self-administer alcohol directly into their stomachs. Such actions indicate that the rats are consuming alcohol for its pharmacological effects, rather than for the benefits of taste, smell, or calories.

At present, researchers have bred several lines of animals that exhibit a preference for alcohol. The use of such animals in alcohol research offers the potential to identify the gene or genes responsible for the alcohol-preferring behavior. For example, using a technique known as subtractive screening, scientists can identify differences in the genes between lines of alcohol-preferring and nonpreferring animals. This research may provide a greater understanding of the underlying mechanisms of alcohol consumption and alcoholism.

Once the genes responsible for alcohol preference are identified, scientists will be able to apply innovative techniques in molecular biology to determine how the presence or absence of a particular gene influences behavior toward alcohol consumption. At present, scientists can use recently developed technology to introduce the gene(s) for alcohol preference (individually or in various combinations) into mouse or rat embryos, producing transgenic animals. If the transgenic animal displays the drinking behavior found in the original animal line, scientists have strong evidence that the transferred gene is involved in the behavioral response under study.

Transgenic animals also may be used to study the regulatory elements of genes. Regulatory elements act as "switches" that turn a gene on or off. For example, by selectively modifying portions of the regulatory elements in alcohol and aldehyde dehydrogenase genes and introducing the altered genes into mice or rats, scientists will be able to observe the changes in expression of the genes under study and the effect of over- or under-production of that enzyme on drinking behavior. Such information also will be valuable to understanding factors that control tissue-specific expression of each gene.

To develop an animal model that parallels the human disease, researchers have been faced with finding animals who actively will seek alcohol.

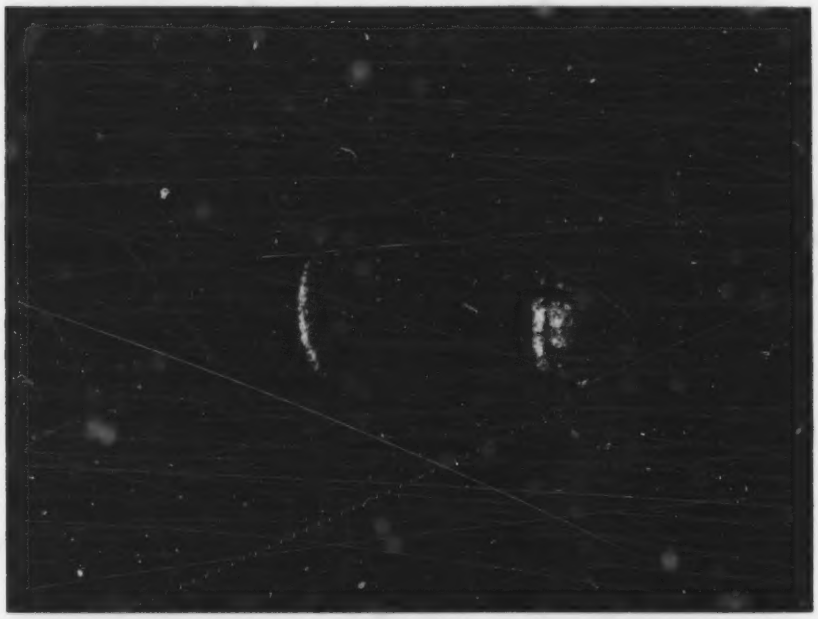
Genetic variations in an individual's response to the effects of alcohol may account for some differences in vulnerability to alcohol abuse and alcohol dependence. The development of selectively bred animals that either prefer or do not prefer alcohol has enabled alcohol researchers to begin to unravel the complex brain mechanisms that control the relationship

between genetic and environmental factors in alcohol addiction.

Although many animal species avoid all but the lowest concentrations of alcohol, alcohol-preferring rats voluntarily administer alcohol (by oral, intragastric, or intracranial routes) for some rewarding effects and will perform various behavioral tasks to gain access to even highly concentrated alcohol solutions. Yet, factors other than genetic susceptibility may contribute to drinking behavior. Through the use of certain behavioral inducements, alcohol-nonpreferring rats can learn to drink increasing quantities of alcohol. Nevertheless, the nonpreferring animals continue to consume far less alcohol than the preferring animals. Over the next few years, researchers will use specially bred animal lines to understand the role of rewarding, anxiety-reducing, and aversive effects of alcohol in the control of drinking.

Animal research also contributes to our knowledge of the medical consequences of alcohol use, including our understanding of alcohol-related fetal injury and fetal alcohol syndrome (FAS). For example, it is recognized that not all women are at equal risk for giving birth to a child with FAS. Evidence (including heightened sensitivity among some racial groups and varying extent of injury in dizygotic, or nonidentical twins) points to the possibility that genetic factors make some women or some fetuses more susceptible and others more resistant to the effects of alcohol. However, these genetic factors remain unidentified. Also unknown is whether the heightened sensitivity is defined by the genes of the mother or of the fetus.

Answers to these important questions can be approached in animal models by coupling genetic breeding with the new technologies of ovum transplantation. Sophisticated genetic breeding studies offer the opportunity to develop animal lines with either heightened or diminished sensitivity to prenatal alcohol. Ovum transplantation, in which a fertilized ovum from one animal strain is placed into the uterus of another strain, offers an important opportunity to localize the maternal and fetal factors that affect the risk for fetal injury.



With new techniques, researchers can isolate and extract a gene from one animal and, as shown above, microinject it into the ovum of a pregnant animal. The developing "transgenic" animal begins to express the newly introduced gene. Photograph courtesy of Dr. Carol Readhead. (Magnification 400x)

The Interaction of Genetics and Environment

As more is learned about alcoholism, researchers are beginning to question whether it is a discrete disease with stable patterns of inheritance. If only one type of familial alcoholism exists and genetic factors are solely responsible for its development, then the incidence of alcoholism in families should remain relatively stable from generation to generation, and changes in environment should have little effect on that incidence. The incidence of sporadic, nonfamilial cases, however, would fluctuate with the presence of various environmental factors, such as increases or decreases in trends of alcohol consumption in the general population.

In a recent study, researchers observed that heightened drinking in the general population leads to both an increase in sporadic cases of alcoholism and a marked increase in the proportion of relatives who abuse alcohol in families of alcoholics. The marked change in populations of individuals who seemingly are genetically vulnerable to alcoholism suggests that social and temporal trends in the use of alcohol influence the observed inheritance of alcoholism.

In the coming decade, gene-environment studies will play a critical role in shedding new light on the genetic and environmental causes of the onset and progression of alco-

holism, adolescent drinking and other high-risk behaviors, and the impact of one person's alcoholism on other persons, such as children of alcoholics, especially with regard to factors that may protect those other individuals from developing alcoholism. From the population studies of the 1970s, which identified a heritable component to alcoholism, to the increasingly sophisticated biological and psychosocial studies of the 1980s, alcohol researchers have continued to refine our understanding of the course of alcohol abuse and dependence. This fine-tuning in our understanding of alcohol-related problems will continue at an increasingly rapid pace throughout the 1990s, spurred by new technological advances and heightened interest of researchers and the lay public alike in preventing and treating these major public health problems.

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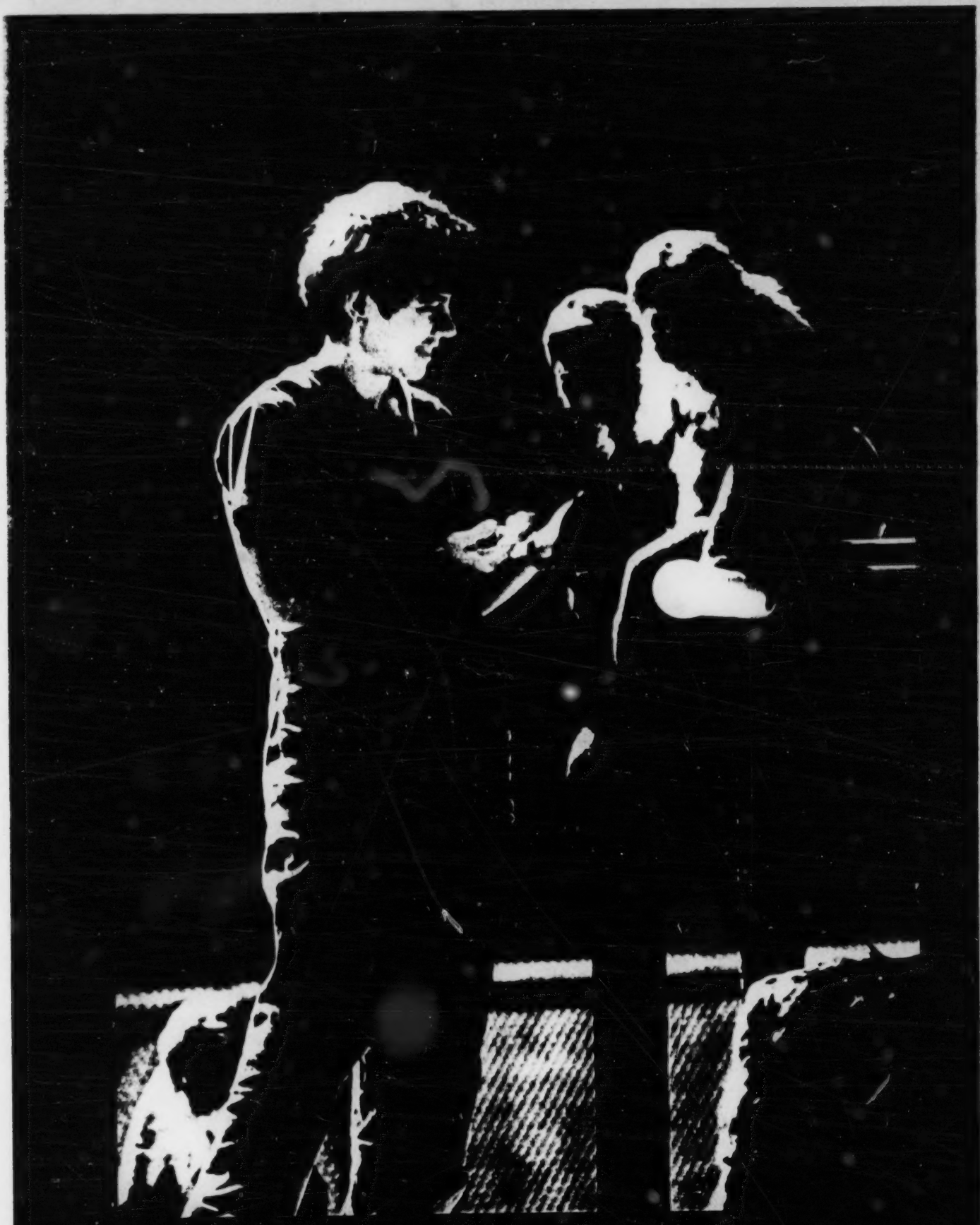


IV Why Do People Drink?

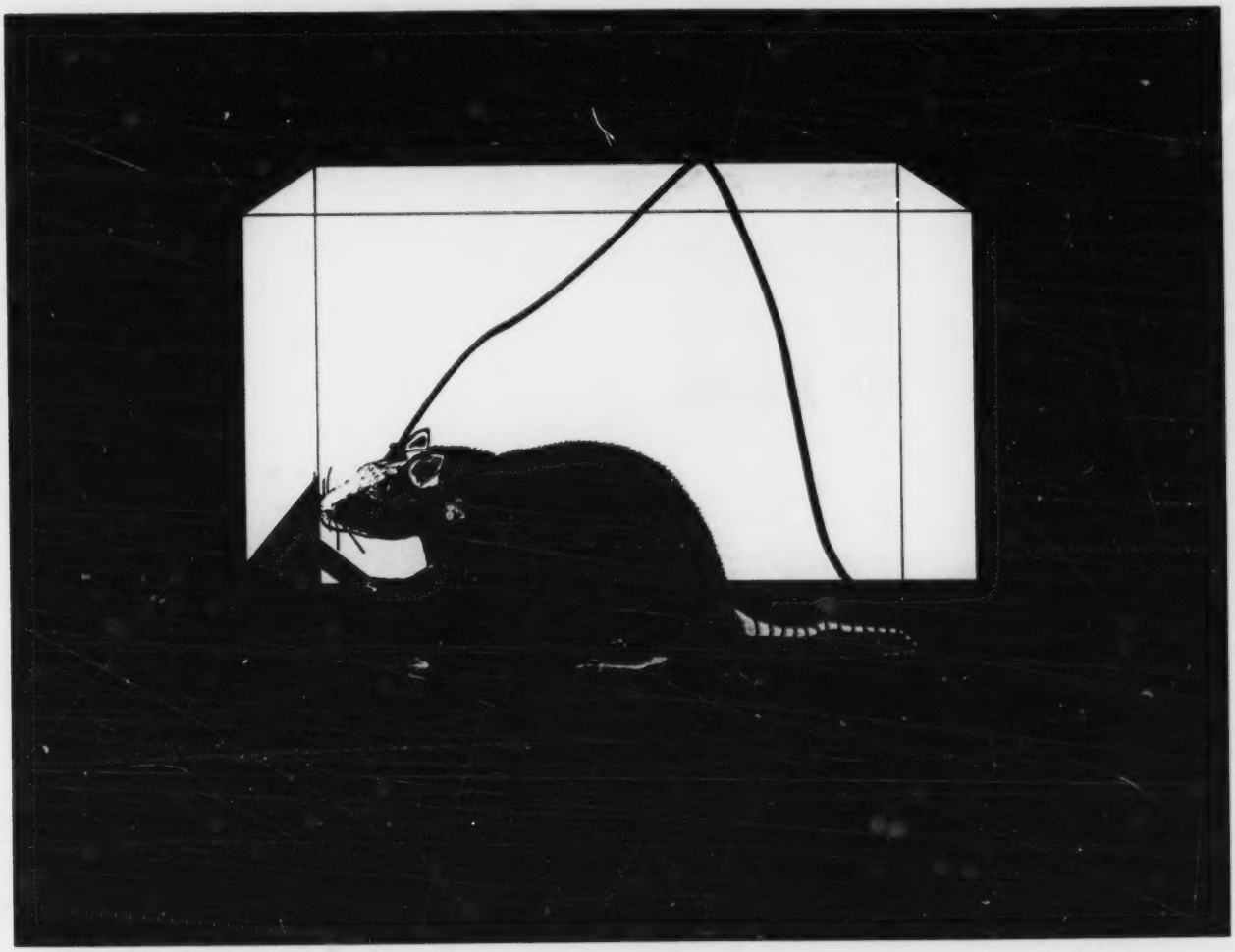
It has long been recognized that individuals tend to repeat behaviors that lead to pleasant outcomes. However, the factors that motivate people to perform an act again and again to gain pleasure or to alleviate discomfort are not yet fully understood.

Scientists use the term "reinforcement" to describe the process in which an effect or outcome increases the chance that a behavior will recur. People learn to perform a behavior, such as drinking alcohol, to obtain a particular outcome, or reinforcer, such as the pleasant (euphoric) or the anxiety reducing (anxiolytic) effect of alcohol. Alcohol researchers are beginning to explore reinforcement in their efforts to understand the processes responsible for alcohol-seeking behavior.

Reinforcement: A Determinant of Drinking

The reinforcing properties of alcohol may explain, in part, why some people drink. Many persons find the effects of alcohol to be pleasant: They experience mild stimulation and a feeling of well-being or reduced anxiety, usually soon after drinking. These effects may reinforce continued alcohol use. At this time, scientists do not understand fully the processes in the body that are involved in the reinforcement of alcohol use. During this last decade of the 20th century, however, researchers hope to gain more knowledge about the nature of alcohol reinforcement and what prompts some individuals to seek repeated exposure to alcohol despite adverse consequences—a behavior that appears to contribute significantly to the development of

Why do people drink? Scientists are using animals to study the processes responsible for alcohol-seeking behavior in humans. Photograph courtesy of Dr. Kathleen Grant.



Researchers use brain stimulation reward studies to examine the nerve circuits in the brain that control reward. Animals learn to press a lever to administer low levels of electric current to specific regions of the brain. This stimulation evokes a rewarding sensation. Drawing by Robert Czechowski and Clare Little.

chronic drinking and dependence and to craving and relapse in patients recovering from alcoholism.

Alcohol researchers have used experimental animals and techniques to study reinforcement and the properties of alcohol that encourage people to drink. One technique, known as brain stimulation reward (BSR), has demonstrated that reinforcement of alcohol-seeking behavior can develop from the property of alcohol that generates a sense of pleasure. This technique has provided valuable information on the nerve circuits in the brain that control reward and, perhaps, euphoria. Findings from a number of different experiments indicate that the neurotransmitter dopamine and its interactions with other neurotransmitters are essential in reward. BSR studies can be used to measure the effect of alcohol on the reward sensation in the brain. Stimulating specific regions of the brain with electrical currents can produce euphoria. In BSR studies, animals work to stimulate their own brains with low levels of electrical current to evoke a rewarding sensation. When these animals are given alcohol, the rate at which they stimulate their brains increases while the amount of electrical current needed to produce reward decreases. Scientists have interpreted these findings to indicate that alcohol increases the euphoria experienced by the animal. This effect, however, is observed only as the amount of alcohol present in the animal's blood is increasing.

Studies with people who consume alcohol in the laboratory have shown that humans also may experience a mild euphoria as the amount of alcohol in the blood increases toward its peak level. This knowledge may help us to understand some of the mechanisms by which euphoria may act to

reinforce alcohol-seeking behavior. If alcohol can produce euphoria only as levels of alcohol in the blood are increasing, people may continue to drink more and more to sustain a pattern of increasing alcohol levels.

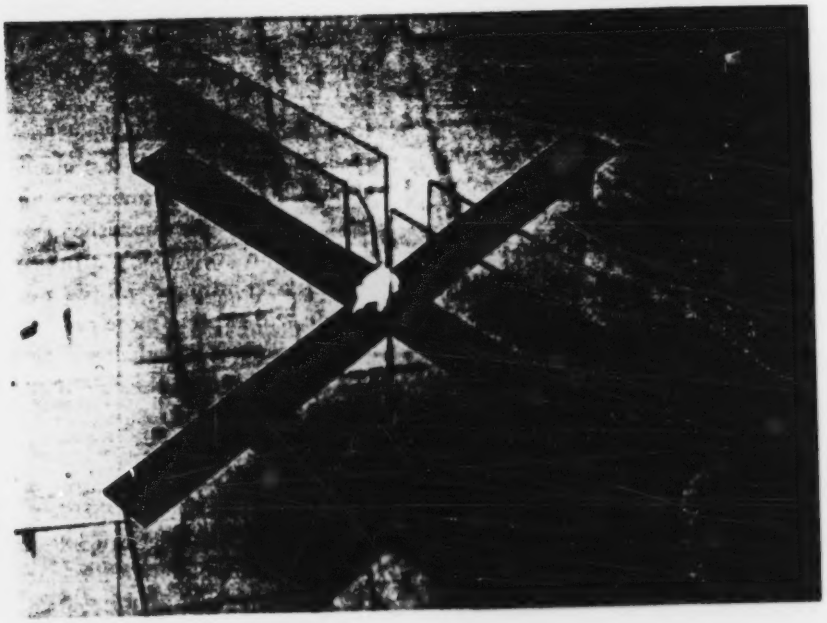
Researchers also have demonstrated the anxiolytic effect of alcohol in studies using animal models and a plus maze technique. A plus maze is a track for animals in the shape of a plus sign. The maze is divided into two sections—one with sides, which shields an animal from open areas; the other without sides, which exposes an animal to the open environment. Experimental animals placed in the maze usually try to remain within the closed area, avoiding the sections without sides.

Following the administration of alcohol, however, the experimental animals will run freely into the open areas of the maze. Moreover, these animals will spend more time in the open regions than the animals that are not given alcohol. Researchers believe that this behavior demonstrates alcohol's anxiolytic effect: Alcohol appears to lessen the anxiety that the animals experience in open spaces.

These observations appear to parallel reports of many individuals who describe diminished tension and anxiety as desirable effects of drinking. The desire to relieve anxiety may contribute to increased drinking and alcohol abuse and promote relapse in abstinent alcoholics.

Alcohol has a unique quality that distinguishes it from other psychoactive drugs and that also may contribute to the reinforcement of alcohol-seeking behavior: It furnishes calories and, thus, may serve as a source of food and energy to the drinker. Although the calories supplied by alcohol are "empty" calories, lacking such essential nutrients as vitamins and protein, they, nevertheless, may substitute as a source of energy and may affect body metabolism. Scientists now recognize that chronic alcohol consumption can affect the normal processes by which our energy and other nutrient needs are met. Accordingly, alcohol problems may be linked to appetite and to appetitive processes.

Researchers have just begun to explore the complex appetitive processes that control hunger, nutritional demands, and thirst. In the



A plus maze is used to study the anxiolytic effect of alcohol. Although rodents normally avoid open sections of the maze, they run freely into these regions after drinking alcohol. This behavior suggests that alcohol may lessen the anxiety that the animals experience in open spaces. Photograph courtesy of Dr. David Goldman.

coming decade, they will work toward determining how alcohol affects these processes and whether alcohol reinforcement is derived, in part, from its food qualities.

Just as some of the effects of alcohol may serve to reinforce continued drinking, other physiological effects of alcohol may deter individuals from alcohol use, thus serving to protect individuals from alcohol abuse and dependence. Alcohol can produce disagreeable, or aversive, effects, such as the extremely uncomfortable symptoms associated with a hangover.

Some individuals experience aversive effects after drinking even small amounts of alcohol. As described earlier, persons of certain Asian origins experience an unpleasant flushing response (reddening of the face and upper chest, hot skin, and increased pulse rate) after drinking alcohol. This response can be sufficiently unpleasant to be a deterrent to excessive drinking.

Scientists are faced with the challenge of determining the importance of such aversive effects in controlling alcohol intake and in bringing about abstinence in alcoholics. In addition, future research may provide insight into the possibility that potential and established alcoholics may be deficient in their ability to experience some of the unpleasant effects of alcohol. These deficits may play a role in the course of their illness.

Psychological and Social Influences on Drinking

How drinking develops, continues, and is modified over time is of considerable importance to understanding the nature of alcoholism and, in turn, to developing both prevention and treatment activities. Researchers studying these issues are using innovative techniques to explore two aspects of drinking behavior: (1) the process by which people learn about alcohol and (2) the ways in which people make decisions about drinking.

Expectancies About Drinking

Drinking behavior cannot be explained solely by the direct pharmacological effects of alcohol that produce euphoria or alleviate anxiety. Other considerations, such as psychosocial factors, learning, and environment, may help to shape drinking behavior.

Scientists have found that an individual's beliefs and expectations about the effects of alcohol on behavior and social functioning play a pivotal role in alcohol use and abuse. Several studies have shown that people who think they are consuming alcohol drink more than those who believe they are drinking a nonalcoholic beverage. Further, both social drinkers and alcoholics who believe they have consumed alcohol behave differently from those who think they have not, even if alcohol has not been consumed.

Expectancy about alcohol use is one factor that may contribute to an adolescent's risk for developing alcohol dependence.

Why is this? One explanation may be that expectancies, which are learned through social processes that transmit information about behaviors and their consequences, are powerful predictors of behavior. Indeed, both adolescents and adults have consistent sets of expectancies about the effects of alcohol on behavior. These expectancies, which are expressed by adolescents as young as 12 to 14 years of age and probably are formed at an even younger age, are predictive of drinking behavior among all age groups. For example, adolescent problem drinkers and adult alcoholics expect that alcohol will improve their mental and physical functioning; yet, their nonproblem-drinking peers do not share this expectancy. Children of alcoholics also hold this expectation of alcohol, whereas their peers, who do not have family histories of alcohol abuse or dependence, do not.

Expectancy about alcohol use is one factor that may contribute to an adolescent's risk for developing alcohol dependence. Learned expectancies may be one way in which risk for alcoholism (that is, family history of alcohol involvement) is translated into problem drinking. Moreover, specific expectancies eventually may be useful for identifying those persons who are vulnerable to developing alcoholism.

Not only can stimuli associated with the taste of alcohol and its pharmacological effects (for example, euphoria) serve as reinforcers of alcohol use; expectancies about drinking experiences also may lead to continued drinking. Expectancies may arise from thoughts of drinking, from pleasant social situations that involve alcohol, and from the anticipation of the euphoria or the diminished anxiety that can accompany drinking. Research conducted in the next decade will explore more fully the mechanisms that underlie expectancy as a reinforcer and the role that it plays in drinking and relapse.

Learning Factors

It is believed commonly that ideas about alcohol and other drugs begin to develop during middle childhood and blossom during adolescence.

Thus, students in the late elementary, middle or junior high school, and early high school years usually are the target group for educational programs on the harmful effects of alcohol and other drugs of abuse. In the past few years, however, alcohol researchers have found evidence suggesting that knowledge about alcohol use is formed much earlier than previously thought.

Investigators have applied innovative techniques from developmental, experimental, and clinical psychology to discover what young children know about alcoholic beverages and drinking behavior. One technique involves showing young subjects pictures of everyday situations in which people are holding a glass or beverage can. The children then are asked to describe what each person is drinking. Results show that children as young as three years of age know that adults consume alcoholic beverages; that children should not drink alcohol; and

Future research studies will examine the family factors that may protect individuals who are at risk for developing alcoholism from developing the disorder.

that men drink alcoholic beverages more often than women. Young children also can correctly identify different alcoholic beverages, and this ability improves with age. Not surprisingly, a significant association exists between the ability to make correct identifications and the level of drinking in the child's home. Thus, educational efforts focused on high-school students may come too late.

Previous research efforts have provided evidence suggesting that attitudes about alcohol are formed early in life. During the 1990s, researchers expect to build on this evidence to make significant advances in charting how young children learn about alcohol and how this knowledge affects subsequent behavior, especially in preadolescent and adolescent children.

Family Influences

Much of our social learning takes place within the family. Hence, scientists have begun to examine the role of family in shaping patterns of alcohol use and abuse. The course of alcoholism often depends on continuing patterns of family life; some family dynamics can reinforce and perpetuate abusive drinking. Marriage or a marriage-like relationship, for instance, has been found to modify the genetic risk for heavier drinking in women.

Alcohol researchers have set as an important goal for the coming decade developing an accurate picture of how family dynamics affects the beginning, continuation, and modification of alcohol abuse. The most important advances in this area of study will address four key issues: (1) the specific ways in which families are disrupted by an alcoholic member; (2) the family and other social factors that protect persons who are at risk from developing alcoholism and the mechanisms by which these factors act; (3) the pivotal role one parent may play in moderating the potentially damaging effects on children of another parent's alcoholism; and (4) the conditions surrounding the onset of adolescent alcohol abuse.

In addition to these issues, researchers will focus on unraveling the increasingly prevalent problems of alcoholism in women. Over the past few years, research findings have suggested that the family processes involved in transmitting and perpetuating alcoholism differ for female and male alcoholics. A greater understanding of these differences will provide new insight into preventing and treating alcoholism in women.

Decisionmaking Processes

Should I drink alcohol? Should I cut back? Should I seek help? Should I have one more for the road? Should I drive after drinking? Should I ride home with my intoxicated date? Drinking alcohol entails many decisions. Some decisions concern drinking itself; others involve managing its consequences. Some are made alone; others are made in social settings. Some are made while sober; others are made while under the influence of alcohol. Moreover, many social responses to alcohol use involve attempts to influence decisionmaking through such efforts as health warning labels, public service announcements, formal educational programs, and legal restrictions on consuming and serving alcohol.

As adolescents test the constraints of their physical and social environments, they make conscious and unconscious decisions to consume or abstain from alcohol.

Studies of decisionmaking processes apply two basic approaches: empirical research and formal modeling. Empirical research examines how people actually make decisions. Formal models, sometimes called decision trees, are used to structure the problem-solving process—that is, to identify and measure risk and to demonstrate how decisions are made.

Research on decisionmaking processes involved in alcohol-related choices among adolescents is exceedingly important. As adolescents test the constraints of their physical and social environments, they make conscious and unconscious decisions to consume or abstain from alcohol. Disruptive family events, parental behavior, peer pressure, and perceptions about community approval may affect their decisionmaking.

Over the next decade, researchers will continue to examine the decisionmaking process and the role of choice in the emergence of alcohol problems. This new wave of research will address such questions as whether processes involved in making decisions about alcohol differ significantly from those that involve other issues. With a better understanding of the decisionmaking process, researchers can identify more effective methods to help individuals make health-promoting decisions about drinking. Further, these studies can assess an individual's perceptions of the risks and benefits of alcohol consumption.

An understanding of decisionmaking processes also may enhance our efforts to establish effective social policies to reduce alcohol-related problems. Economists have theorized that a model of "rational addiction" can describe decisionmaking involved in addictive behavior. This approach

emphasizes the effects of prices on drinking choices. The model postulates that even alcoholics may be influenced by the pattern of prices for alcoholic beverages. Moreover, the effect of price on drinking behavior is dynamic (that is, lower prices may contribute to increased drinking that strengthens an addiction and leads to increased drinking in the future). Temporary price increases may affect behavior differently than permanent increases. In addition, drinking behavior may change with an anticipated rise in prices. Although preliminary studies exploring this concept have provided promising results, more research is needed. The knowledge gained from these studies will be useful in the continuing search for effective policies to reduce the personal and social costs of addiction.

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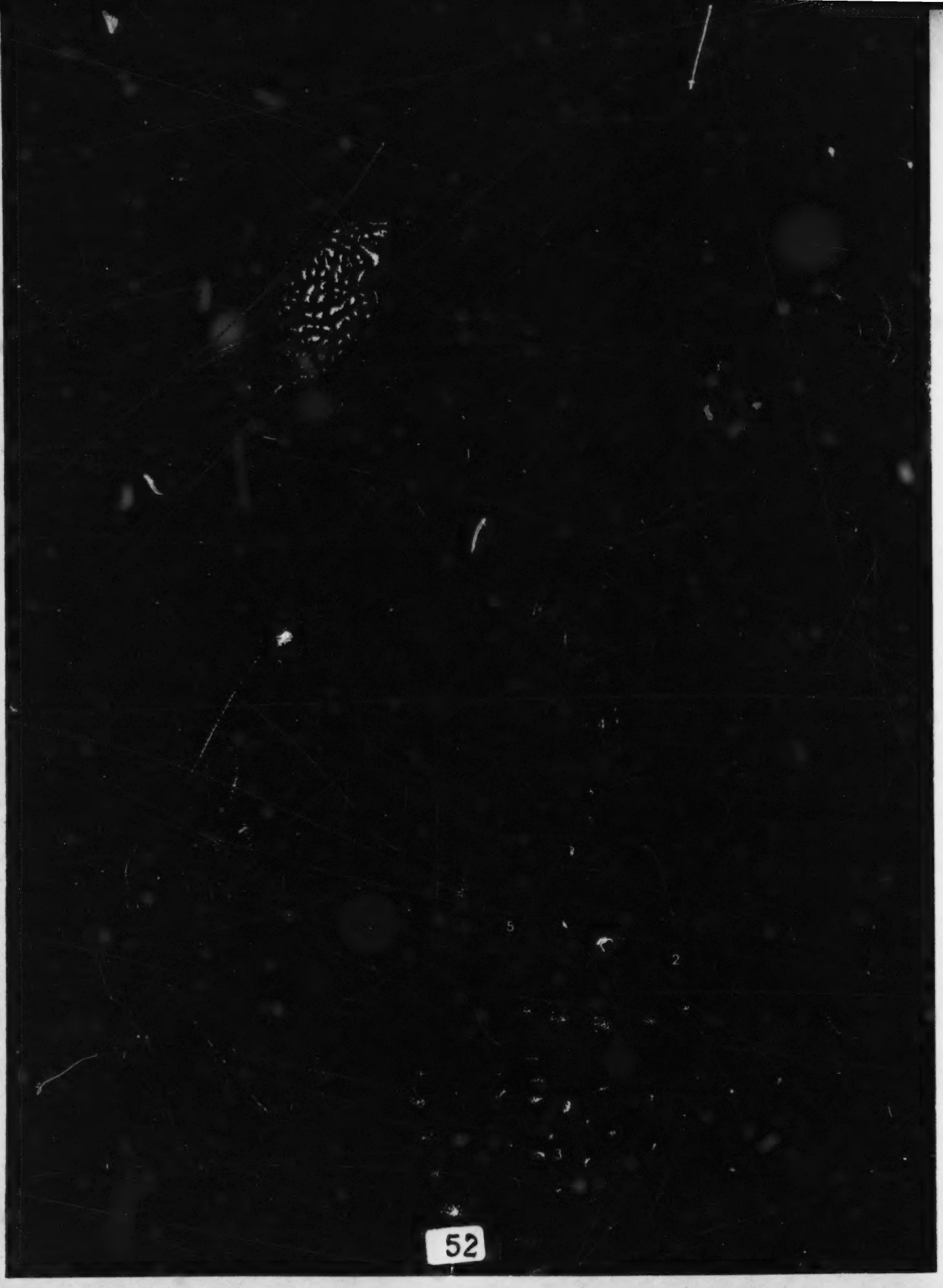


V THE MEDICAL CONSEQUENCES OF ALCOHOLISM

Liver disease, pancreatitis, cardiovascular disorders, and brain damage are just several of the many disorders resulting from chronic drinking that clinicians often see in the patients they treat. Virtually no part of the body is spared the harmful effects of excessive alcohol consumption.

Although, at present, no proven mechanisms explain completely how alcohol exerts its effects to produce the multitude of diseases associated with heavy drinking, evidence suggests that a number of factors contribute to the development of alcohol-induced disorders. Susceptibility for developing alcohol-related diseases seems to vary from individual to individual. Although much of the evidence is preliminary, researchers now are finding that genetic factors may play a significant role in defining an individual's vulnerability.

Yet, genetic factors, alone, may not fully account for varying susceptibility to developing diseases associated with alcohol abuse. It appears that complex relationships exist between the development of alcohol-induced damage and the amount, duration, and pattern of consumption. The frequency of drinking, the duration of drinking bouts, the blood alcohol concentration attained in the drinker's body, and whether the pattern of drinking permits time for the body to recover before drinking resumes are likely to be important risk determinants for the development of alcohol-related diseases. Alternatively, researchers may discover that the total lifetime exposure to alcohol is more important to defining risk than the number of times an individual attains relatively high blood or organ alcohol concentrations.

Cofactors also may influence an individual's vulnerability for alcohol-induced organ damage. Although alcohol is the primary cause of most

When alcohol is consumed, it passes through the esophagus (1) and into the stomach (2), where small amounts are absorbed. Most of the alcohol ingested, however, passes to the small intestine (3), and is readily absorbed into the bloodstream with other nutrients. Distributed throughout the body in the blood, alcohol affects various organs and systems, including the heart (4) and cardiovascular system. Although moderate drinking may have some beneficial effects on the cardiovascular system, heavy drinking eventually can cause the heart muscle to deteriorate. Digested food substances and alcohol are carried away from the small intestine to the liver (5), the primary site for alcohol metabolism. In the liver, enzymes metabolize alcohol to carbon dioxide and water. Painting by Edward S. Gazsi. Reprinted from National Geographic Magazine 181(2), 1992.

alcohol-related diseases, the presence of other diseases or conditions, such as infections or nutritional deficiencies, may increase an individual's chance of developing one of the many diseases that result from alcohol's deleterious effects on the body's organs and systems.

It is still unknown why only certain people who drink develop alcohol-related diseases. Despite decades of slow progress in studying and treating alcohol-related diseases, however, we now can approach these problems with increasing optimism. Recent research, such as evidence for the possible role of genetic factors in the development of alcohol-related pathologies, should produce rapid advances in treatment in the future.

Alcohol and the Liver

The largest organ of the body, the liver performs many essential functions: It filters circulating blood; it secretes bile into the gastrointestinal tract; and it synthesizes proteins and other organic compounds vital to the body. Because the liver plays a critical role in many fundamental activities within the body, injury to this organ can produce a wide range of serious medical consequences.

As the primary site for alcohol metabolism, the liver is particularly vulnerable to injury from chronic alcohol consumption. Because liver diseases are prevalent among heavy drinkers, efforts to understand the basic mechanisms responsible for alcohol-induced liver damage are a priority for alcohol researchers.

When alcohol is consumed, it passes through the esophagus and stomach to the small intestine, where it is readily absorbed with other nutrients. Digested food substances and alcohol then are carried from the small intestine to the liver, entering by way of the portal vein. By acting selectively upon the digested material, the liver can remove toxic substances from the circulating blood.

Once alcohol reaches the liver, it is metabolized initially to acetaldehyde. Acetaldehyde is broken down rapidly to acetate which, in turn, is converted to carbon dioxide and water. Because acetaldehyde is highly toxic to the liver and to other organs, its conversion to acetate is an extremely important metabolic step. It has been suggested that the elevated levels of acetaldehyde often found in heavy drinkers may cause the alcohol-mediated injuries frequently seen in these individuals.

Chronic and heavy drinking can cause significant damage to cells in the liver. Cellular injury is presented as fatty liver, alcoholic hepatitis, or cirrhosis.

Fatty liver, a relatively benign and reversible condition that is common to alcoholics, usually indicates recent drinking. The condition is marked by the accumulation of fat in the liver that causes the organ to become enlarged. Abstinence usually leads to complete reversal of this abnormality.

As the primary site for alcohol metabolism, the liver is particularly vulnerable to injury from chronic alcohol consumption.

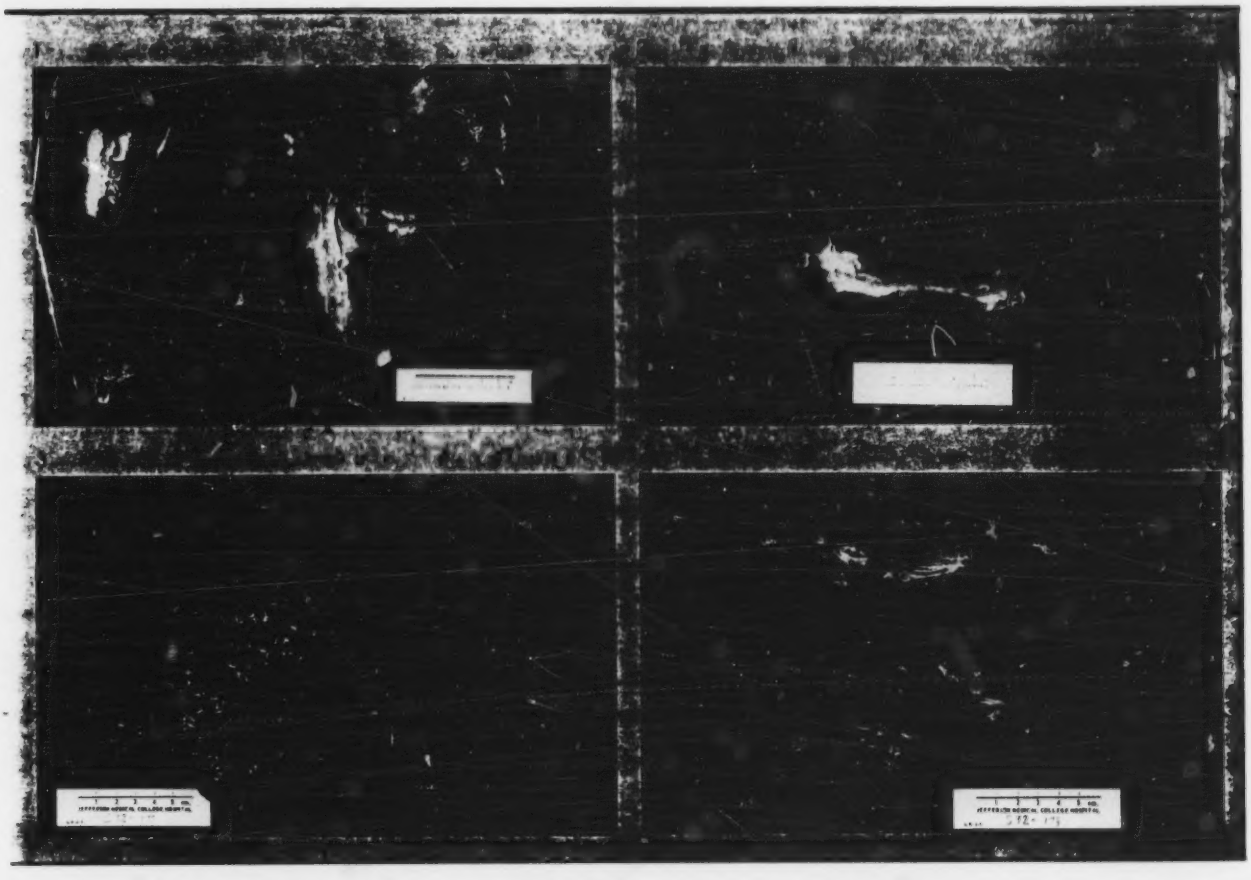
Alcoholic hepatitis, a considerably more serious condition, is marked by widespread inflammation of the liver and increasing destruction of liver tissue. In its most severe form, this condition can be life-threatening. Healing usually occurs with abstinence, although there may be residual scarring.

Cirrhosis is an extremely grave and irreversible disease that accounts for over 26,000 deaths each year. In 1986 (the last year for which data are available), this disease was ranked as the ninth leading cause of death in the United States. Characterized by a progressive replacement of healthy liver tissue with diffuse scarring, cirrhosis can lead to death from liver failure if drinking continues. However, if a cirrhosis patient becomes abstinent, the proliferation of scar tissue subsides, and the individual's life can be prolonged.

Impaired liver functioning also may have profound effects on other organs and systems in the body. Primary hepatic encephalopathy, a brain dysfunction associated with alcoholic hepatitis and cirrhosis, is an example of such an effect. This condition, which is marked by altered intellectual function and emotion, as well as by disturbed psychomotor and behavioral regulation, appears to develop as a consequence of the liver's inability to perform its many vital functions.

Immune Responses in Liver Damage

Alcohol can damage the liver directly or through a series of complex biochemical interactions that cause the body literally to attack itself. The metabolite acetaldehyde is a highly reactive compound that combines chemically with various proteins and cell membrane components to form products known as adducts. When naturally occurring proteins combine with acetaldehyde, their physical and chemical properties become altered and they appear foreign to the body's immune system. As a result, the immune system generates antibodies to attack and remove these proteins.



(1) A healthy liver. (2) Cross-section of a healthy liver. (3) A cirrhotic liver. Cirrhosis is characterized by diffuse scarring of the liver. (4) Cross-section of a cirrhotic liver. Photographs courtesy of Dr. Emmanuel Rubin.

According to a recent study, 70 percent of alcoholics have antibodies to acetaldehyde adducts. Antibody levels are especially high in patients with alcoholic hepatitis, suggesting that immune response to acetaldehyde adducts is involved in the development of alcoholic liver disease. Moreover, acetaldehyde adducts appear to interfere with proper functioning of important liver proteins. Thus, the presence of these adducts, alone, may contribute to the development of alcoholic liver disease.

Scientists also are examining the role of cytokines in alcoholic liver disease. Cytokines are a class of small proteins, produced by white blood cells, that serve as cell messengers and hormones. Elevated levels of a specific cytokine, called tumor necrosis factor alpha (TNF alpha), mark the presence of alcoholic liver disease and may be involved in its development. Recent studies have shown that TNF alpha production is abnormally high in alcoholic hepatitis patients, even when they are not drinking. Moreover, elevated TNF alpha levels in alcoholic hepatitis patients appear to be highly predictive of early death.

Whether TNF alpha plays a direct role in the development of alcoholic hepatitis remains unresolved. The production of this cytokine may be the immune response triggered by the acetaldehyde adducts present in patients with alcoholic liver disease and, further, may be the mechanism by which alcohol causes liver disease.

If cytokines, such as TNF alpha, are identified as causative factors for alcohol-induced liver disease, medications that selectively block this

immune response may be developed, thereby lessening or eliminating at least one factor involved in liver disease. Ultimately, such medications could impede the progression of this serious alcohol-related disease.

Research on the involvement of immune response in alcoholic liver disease is still new and requires more detailed study in the future. For example, it is not known whether genetic factors that control immune response to acetaldehyde adducts play an important role in explaining why only a percentage of heavy drinkers develop alcoholic hepatitis. Gaining a fuller understanding of the nature of genetic risk factors will enable alcohol researchers and clinicians to more effectively prevent and treat alcoholic liver disease.

Oxygen Availability

Researchers are attempting to determine whether mechanisms other than immune response may be involved in the damaging effects of alcohol on the liver and the subsequent development of liver disease. At present, the role of oxygen deprivation in the liver is being explored as a causative factor for liver disease. When an individual drinks heavily, the liver requires increasing amounts of oxygen to metabolize the alcohol. Thus, oxygen may be diverted from other functional processes in the liver to allow the organ to carry out alcohol metabolism. However, diverting the oxygen to alcohol metabolism may deplete liver cells of critical oxygen supplies needed for other vital functions. The resulting diminished oxygen quantities may provoke injury to the liver. Moreover, the presence of anemia or blood flow obstructions in the liver (conditions not uncommon among alcoholics with liver disease) may exacerbate oxygen deprivation.

Adding to this process of potential liver injury is the finding that alcohol dehydrogenase, a primary metabolizing enzyme that converts alcohol to acetaldehyde, is more abundant in regions of the liver far away from the entry point of oxygenated blood to the organ. Thus, the region where alcohol may provoke oxygen deficiencies also is the site where acetaldehyde adducts can form.

In addition, oxygen deprivation from alcohol metabolism may decrease the rate at which fatty acids are broken down. This rate, normally reduced in low-oxygen regions of the liver, would be much reduced in the presence of alcohol. The effect of alcohol on this process may explain why low-oxygen regions are the sites of fat deposits in heavy drinkers with fatty liver. All of these phenomena are consistent with the observation that alcohol-induced injury most frequently occurs in liver regions with limited oxygen availability.

Researchers are attempting to determine whether mechanisms other than immune response may be involved in the damaging effects of alcohol on the liver.

Genetic Susceptibility

Clinicians have observed that some heavy drinkers do not develop liver disease, even though these individuals may drink as much as others who do develop liver disease. This observation has prompted researchers to question whether genetic factors may play a role in susceptibility to liver injury. Evidence that supports this idea, which includes studies of identical twins, has shown that if one member of the pair has alcoholic cirrhosis, the other member is more likely to develop this disease than are other siblings.

The disproportionate number of deaths from alcoholic liver disease in women compared with men provides more evidence for a genetic risk factor for alcohol-induced liver injury. Findings suggest that the detrimental effects of alcohol on the liver are more severe for women than for men: Women who drink heavily develop liver disease after a comparatively shorter drinking period and at a lower level of daily drinking than men.

Although the reasons for varying susceptibility between the sexes are not known, gender specific variation in alcohol metabolism may contribute to the heightened vulnerability to alcoholic liver disease in women. A recent study found that alcohol dehydrogenase (ADH), a primary enzyme in alcohol metabolism, is expressed in the stomach in lower levels in women than in men. Diminished levels of ADH in women result in decreased metabolism of alcohol, and increased amounts of alcohol in the blood. The resulting elevated levels of blood alcohol may contribute to women's seemingly heightened susceptibility to alcoholic liver disease.

The genetic mechanisms involved in the production of collagen—a structural protein and the major protein found in liver scar tissue—also may be a link to understanding disparate susceptibility to alcoholic liver disease. Collagen is not a single protein; the body produces at least 10 different types. Although this structural protein is found in the healthy liver, the amount increases dramatically in cirrhosis. Recent findings suggest that

individuals with alcoholic cirrhosis may produce a unique variant of one of the collagen genes, known as type I collagen.

However, the significance of this finding in understanding genetic vulnerability to alcoholic cirrhosis is unclear. Perhaps this variant gene is a marker, identifying individuals who have heightened vulnerability to cirrhosis. In studying this gene, researchers may gain greater insight into the mechanisms involved in the development of alcoholic cirrhosis and, in turn, may apply this knowledge to improve approaches aimed at preventing and treating alcohol-induced injury to the liver.

Alcohol's Damaging Effects on the Pancreas

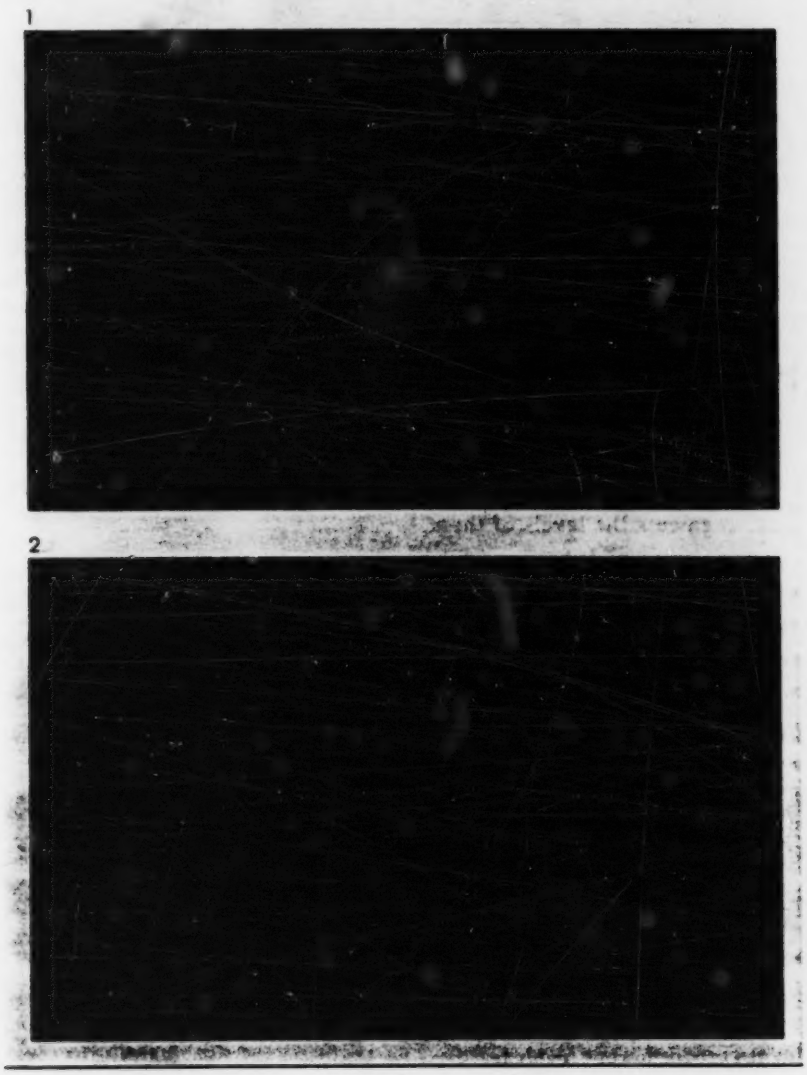
The pancreas, a large, elongated gland positioned behind the stomach, serves as an accessory digestive organ that assists in the breakdown of ingested foods. It accomplishes its digestive function by secreting into the small intestine specific enzymes that catalyze the breakdown of carbohydrates, proteins, and fats. In their chemically simpler forms, these nutrients can be absorbed easily by the small intestine.

In addition to its digestive role, the pancreas also functions to maintain blood sugar levels. Insulin and glucagon, two hormones synthesized and released by the pancreas, act conjointly to regulate blood sugar levels within a rather narrow range, despite wide fluctuations in sugar intake.

More than three-quarters of patients with chronic pancreatitis—a painful inflammation of the pancreas—have a history of heavy drinking. Pancreatitis, which typically appears after 5 to 10 years of excessive drinking, produces severe abdominal pain that can recur even if drinking ceases. Sometimes the pain associated with this disease can be relieved only by removing the pancreas surgically. However, well before the onset of pain, the disease is present and is producing chronic changes in the organ.

The association between alcohol abuse and chronic pancreatitis has prompted researchers to question how alcohol adversely affects the structure and function of the pancreas. Alcohol stimulates the production of pancreatic digestive enzymes. This effect, combined with an obstruction of enzyme flow through the pancreatic duct leading to the small intestine, augments the levels of these digestive enzymes. It has been suggested that these digestive enzymes may become activated in the pancreas rather than in the small intestine, where enzyme activation normally occurs, resulting in digestion of the pancreas by its own enzymes. Such events may be responsible for the development of pancreatitis in heavy drinkers.

Recent research has provided new insights into the mechanisms involved in the development of this disease. Evidence from animal studies indicates that alcohol's action in increasing the production of a highly reactive form of oxygen, called oxygen free radicals, may be one of the underlying causes of pancreatitis. In experimental studies, allopurinol—a drug that appears to block free radical formation—significantly reduced the severity of the disorder. Further, agents that destroy free radicals once they are formed also produced favorable effects. Broadening these new findings through continued research may enable scientists to develop more effective treatment approaches and prevention strategies for this painful and debilitating disease.



(1) Biopsy of a healthy heart. (2) Biopsy of heart muscle from an asymptomatic alcoholic patient shows fibrous tissue and enlarged muscle cells. Photographs courtesy of Dr. Emmanuel Rubin.

Alcohol's Effects on the Cardiovascular System

The Heart

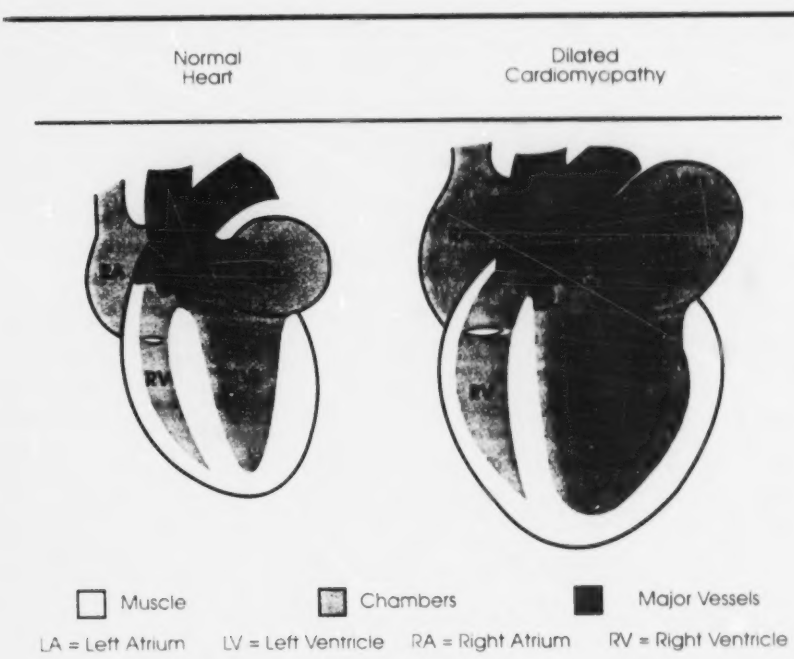
Alcohol's toxic effect on the heart is dose dependent: As total lifetime alcohol consumption increases, muscular strength decreases. Clinical tests show that alcohol can cause the heart muscle to deteriorate, leading to a condition known as alcoholic cardiomyopathy. Characterized by a wasting of the heart muscle, alcoholic cardiomyopathy is one of the most serious consequences of drinking and can be fatal. With this condition, contractility of the muscle cells decreases, predominantly in the left ventricle of the heart (the chamber that pumps oxygenated blood to the body). As cardiac muscle fibers become damaged or die, the heart attempts to compensate for the injury by increasing in bulk and size. Although this adaptive response remedies the impaired functioning for a time, eventually the heart becomes unable to pump sufficient amounts of blood to meet the needs of the body. Abstaining from drinking, however, can help patients with alcohol-induced heart disease to recover.

Until recently, physicians did not suspect that weakness of the heart muscle occurs in alcoholic patients who do not manifest the clinical signs of alcoholic cardiomyopathy. New evidence suggests, however, that cardiac function may be impaired in a substantial number of alcoholics.

Although alcohol's toxic effects on the heart have been demonstrated, scientists continue to search for the mechanisms responsible for these damaging actions. Researchers have found that impaired functioning may result from the disruptive effect of alcohol on metabolic pathways in the heart. Alcohol is metabolized within the heart to a class of compounds known as fatty acid ethyl esters—compounds that have the potential to impede functioning of the mitochondria (the energy producing structures in the cell). The effect of alcohol on this metabolic pathway may explain how alcohol abuse can lead to diminished cardiac muscle contractility and to cardiomyopathy.

In addition, animal studies have revealed that alcohol appears to impair the uptake and binding of calcium ions needed for muscle contraction. These observations suggest that alcohol's actions on calcium levels in cardiac muscle cells may contribute to the reduced strength of cardiac contractions associated with alcohol abuse.

Although the effects of alcohol are apparent with the observable damage on heart structure and function, scientists are just beginning to identify and characterize the underlying molecular mechanisms. As greater knowledge of



A heart in dilated cardiomyopathy, compared to a normal heart.

these mechanisms is gained through future research efforts, clinicians will be able to better prevent and treat the cardiac disorders associated with alcohol abuse.

The Vascular System

In addition to possible direct effects on the heart, alcohol also may affect the vascular system—the system of blood vessels extending throughout the body. By affecting the release and actions of hormones and other regulatory substances (such as catecholamines and cortisol, among others), alcohol may modify cardiac activity, blood pressure, and blood flow. Ultimately, such changes may damage the heart and vascular system.

Hypertension—the persistent elevation of blood pressure—is a serious illness that can be caused or aggravated by alcohol use. Chronic drinking leads to hypertension, although, when small doses of alcohol are consumed, peripheral blood vessels dilate and blood pressure falls. In fact, in many studies, hypertension is apparent at the level of three or four drinks a day. Hypertension is a known risk factor for hemorrhagic stroke and other disorders.

As scientists continue to search for the mechanisms involved in alcohol-induced hypertension, several hypotheses are being explored. For example, alcohol consumption is associated with the loss of large quantities of calcium and magnesium ions in the urine. Reduced levels of magnesium cause hypertension in both animals and humans. Further, diminished magnesium levels are associated with increased amounts of calcium—an element that heightens the tone of blood vessels, leading to hypertension. Alcohol-induced magnesium depletion may promote spasms in brain blood vessels, impeding blood flow to the brain. This mechanism may contribute to the development of hypertension in chronic drinkers.

Clinical studies have demonstrated that a higher incidence of hemorrhagic stroke and other intracranial bleeding exists among heavy drinkers than

among nondrinkers. Scientists have suggested that alcohol-associated hypertension and a bleeding tendency due to heavy alcohol use both may contribute to the development of hemorrhagic stroke.

In a recent large-scale study, scientists examined the relationship between alcohol consumption and the risk for coronary artery disease in males. Investigators monitored approximately 45,000 men over a 2-year period, excluding from the study individuals with pre-existing health conditions that could increase the risk of heart disease. Researchers found a decreased incidence of coronary artery disease in individuals who drank approximately two to three drinks per day. Yet, these consumption levels did not have a favorable effect on hypertension: The occurrence of hypertension was greater in heavier drinkers than in lighter drinkers. More studies are needed to determine conclusively whether moderate drinking is the factor that contributes to diminished incidence of coronary disease.

Even if moderate drinking lessens the risk for coronary artery disease, such drinking can harm other organs in the body. In addition, the interaction of alcohol with medications that a moderate drinker may be taking can produce very serious outcomes. Finally, moderate drinkers risk enhanced liability to addiction and behavioral changes that may threaten their safety or that of other persons.

Neurological Disorders Associated with Alcohol Abuse

It is well documented that excessive drinking can harm the brain; the damage often becomes evident with distinct behavioral and cognitive changes in the drinker. For example, an alcoholic may experience blackouts, seizures, and hallucinations as a consequence of alcohol's injurious effects on the brain. Moreover, heavy drinking can seriously impair a person's ability to remember and to perform intellectual tasks. The type and severity of the brain damage linked with alcohol abuse, however, can vary depending upon a person's genetic vulnerability, age of onset of drinking, the type and amount of alcohol consumed, and diet.

Scientists have found that alcohol can harm the brain in a number of ways. Damage can result directly from alcohol's toxic effects on the brain. Further, alcohol-related damage to other organs, such as the liver, pancreas, and heart, can impair proper brain functioning. Finally, poor dietary habits that frequently accompany chronic drinking can lead to nutritional imbalances that, in turn, can impair the nervous system. The cellular and molecular mechanisms involved in alcohol-induced brain injury are unknown. Because the brain not only governs basic responses but also is the center of such human faculties as thinking, abstracting, emotions, and memory, any damage—mild or severe—can have a far-reaching impact on a person's daily activities. Thus, gaining knowledge about alcohol's actions on the brain continues to be an important goal for alcohol researchers.

Cognitive Function

Approximately 45 to 70 percent of alcoholics entering treatment display some difficulty with problem solving, abstract thinking, psychomotor performance, and difficult memory tasks. Scientists continue to search for the mechanisms that underlie these impairments. The recent development of imaging techniques has enabled researchers to identify certain structural abnormalities—possibly resulting from alcohol abuse—that may account for the impaired intellectual and memory functions in many alcoholics. In addition, autopsy studies have shown that alcoholics have general brain atrophy as well as specific cell loss in at least two structures of the brain that control memory.

Heavy drinking also alters certain biochemical mechanisms in the brain that may impede cognitive and memory processes. The loss of receptors for the neurotransmitter acetylcholine in the brain's frontal cortex is among the many alcohol-related biochemical disturbances under investigation. This loss could disrupt the transmission of messages between neurons in the brain, thereby causing varying degrees of impaired memory and learning.

Organic Brain Disorders

Two types of organic brain syndromes may develop in alcoholics: alcoholic dementia and Wernicke-Korsakoff's syndrome. Approximately 10 percent of patients in alcoholism treatment display symptoms of these disorders.

Alcoholic dementia is characterized by a global loss of intellectual abilities. Physiological and structural abnormalities are evidenced by electrophysiological and brain imaging techniques. All of these impairments are considered direct effects of alcohol's neurotoxicity. Research findings suggest that some individuals may be more vulnerable genetically than others to alcohol's injurious effects on the brain.

Wernicke's disease is an alcohol-related brain degeneration that produces general confusion, abnormal gaze and gait, loss of muscle coordination, and incoherent speech. This disorder is associated with a deficiency of the vitamin thiamine, which is needed for cellular energy production. Abstinence and vitamin supplementation can reverse this disorder.

In the acute stage, Wernicke's disease often occurs with Korsakoff's encephalopathy and patients are diagnosed as having Wernicke-Korsakoff's syndrome—characterized by a permanent state of cognitive dysfunction and an inability to remember recent events or to learn new information. The amnesia may result from widespread lesions and structural aberrations throughout the brain. Although amnesia is the most clearly defined symptom, Wernicke-Korsakoff's patients also may have limited attention, perception, motivation, and emotion.

Genetic Susceptibility

It is well recognized that Wernicke-Korsakoff's syndrome develops in some individuals following a history of chronic and heavy drinking. At present, however, it is unknown how alcohol causes distinctive injury to the brain. Given the grave consequences of Wernicke-Korsakoff's syndrome, researchers and clinicians are quite eager to identify the mechanisms involved in its development.

It has been suggested that some individuals may have a genetic susceptibility to developing Wernicke-Korsakoff's syndrome involving an enzyme that requires thiamine for its function. Research has shown that alcoholics with Wernicke-Korsakoff's syndrome may have a defective variant of the naturally occurring enzyme transketolase. The variant form of this enzyme (which is a genetic defect) has an abnormally weak affinity for thiamine. Thus, vulnerability to this syndrome may be linked to the genetic defect in the transketolase enzyme gene and may be exacerbated by a dietary insufficiency of thiamine.

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VI Fetal Alcohol Syndrome

Throughout the course of history, a number of clinicians have noted the potentially harmful effects of alcohol on a developing fetus. Their observations and concerns appear to have passed unheeded.

It was not until 1968 in France—and 1973 in America—that scientists first described in published reports the common pattern of birth defects in children born to mothers who drank heavily during pregnancy. Labeled "fetal alcohol syndrome" (FAS), this congenital disorder is characterized by a distinct cluster of symptoms, including permanent physical abnormalities and mental retardation. The recognition of FAS set in motion research efforts to answer such critical questions as:

- How extensive is the problem of FAS?
- What is the relationship between quantity and frequency of maternal alcohol use and risk to the developing fetus?
- Can drinking during pregnancy result in pathology less severe than that of FAS?
- What is the potential for preventing injury in pregnancy, reversing injury in pregnancy, or both?
- What are the physiological mechanisms by which alcohol causes fetal injury?
- How do additional risk factors (number of previous pregnancies, other drug use by the mother) influence the effect of alcohol on the developing fetus?

FAS is one of the leading known causes of mental retardation. According to research estimates, 1 to 3 babies are born with FAS for every 1,000 live births. Among the population of known alcoholic mothers, the rate of FAS increases substantially to a

Prenatal exposure to alcohol can produce a wide spectrum of consequences in the fetus, ranging from the severe physical and mental impairments seen in FAS children, to the less prominent clinical features seen in those identified with FAE, to the various behavioral and learning problems observed in other children whose mothers drank during pregnancy.

range of 23 to 29 FAS babies for every 1,000 live births.

Initially, researchers questioned whether alcohol was the underlying cause of FAS, or whether another factor believed to be present in an alcoholic woman (poor nutrition, other drug use, or inadequate prenatal medical care) was the antecedent. Animal studies that enabled scientists to control for all factors other than alcohol established that alcohol actually is a teratogen—an agent that produces defects in offspring before birth. Researchers now have identified a wide spectrum of consequences resulting from prenatal alcohol exposure, ranging from the severe physical and mental impairment in FAS children, to the less prominent clinical features seen in children diagnosed as having fetal alcohol effects (FAE), to the various behavioral and learning problems observed in other children whose mothers drank during pregnancy.

Children with FAS exhibit growth deficiencies that persist throughout childhood. These children have a characteristic cluster of facial features that includes small and widely spaced eyes and underdeveloped upper lips and mid-facial regions. Serious neurological and behavioral problems, such as intellectual impairment and mental retardation, also are present. Occasionally, FAS children have less specific malformations, such as cardiovascular anomalies, genitourinary defects, and muscle abnormalities.

Although FAS appears to occur exclusively in babies born to mothers who are heavy drinkers or alcoholics, researchers have not defined a safe level of drinking during pregnancy. Even moderate maternal drinking may pose risks to a developing fetus, perhaps resulting in subtle effects in offspring. The damaging effects of prenatal exposure to alcohol, so apparent in children with FAS and FAE, can be prevented with maternal abstinence during pregnancy.

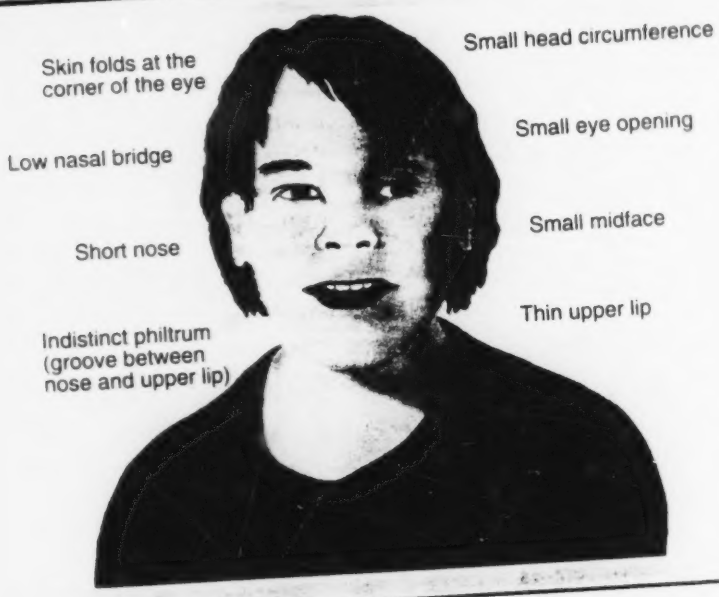
Still, women who are alcohol dependent sometimes drink while pregnant despite a strong desire to abstain. Many other women also may drink and expose the developing embryo to alcohol in the early phase of pregnancy, before they are even aware that they are pregnant. The consequences that can result from these actions underscore the importance of continuing research dedicated to identifying and characterizing the mechanisms by which alcohol causes injury to the fetus. Toward this goal, scientists are exploring such critical issues as the timing of exposure to alcohol throughout pregnancy, select maternal factors, effects of alcohol on the placenta, and alcohol's direct actions on the developing fetus. The knowledge obtained from this research can augment efforts to prevent future injury to the unborn child and enhance the development of treatment approaches for alcohol-induced injuries that occur in children exposed prenatally to alcohol.

Even moderate maternal drinking may pose risks to a developing fetus, perhaps resulting in subtle effects in offspring.

Although drinking during pregnancy is never risk-free, it appears that the type of injury that results from alcohol use does depend on the prenatal period when alcohol is consumed. In studies with primates, researchers found that injury to the offspring was more severe when alcohol was administered at the beginning of pregnancy as opposed to the fifth week of gestation. Additional research with animals has shown that the fetal nervous system may experience significant injury when alcohol is consumed during the "brain growth spurt" interval—a period that is equivalent to the latter half of pregnancy in humans.

Scientists still do not know whether the risk of harm to the fetus is associated with the total amount of alcohol consumed by the mother during pregnancy, regardless of the time interval for drinking, or with the maximum level of alcohol in the blood at given times. Although animal studies suggest that the maximum amount of alcohol in the blood is by far the more important of the two risk factors, the time period in which alcohol is consumed also is an important risk determinant for the human fetus. The importance of drinking time schedule on fetal outcome became apparent in animal studies in which the same amount of alcohol was given to animals over an 8-, a 12-, or a 24-hour period. Researchers found that the more compressed the time schedule, the more devastating the harm that was caused to the fetus. In human terms, if two pregnant women each consumed seven drinks per week—the first drinking all seven drinks during two weekend evenings and the second drinking one drink on each of the 7 days in the week—the first woman would place her child at far greater risk for injury than the second woman.

Research has revealed that alcohol-related fetal injury may stem from alcohol's actions on the placenta (the organ that links the mother to the developing baby and provides sustenance and protection to the fetus throughout prenatal development). It has been observed that alcohol, at relatively modest concentrations, can


Skin folds at the corner of the eye
Small head circumference
Small eye opening
Low nasal bridge
Small midface
Short nose
Thin upper lip
Indistinct philtrum (groove between nose and upper lip)

Children with FAS have characteristic facial features. Artist's rendition by James Sottile, Jr.

induce a brief collapse of the blood vessels that support the uterus and fetus. Such a collapse could lead to shortages in nutrients and oxygen supplies essential to fetal development, causing injury to the fetus. Additional research in this area in the coming years potentially will pinpoint how alcohol affects the placenta and which steps may be taken to reduce the risk of subsequent injury to the fetus.

Various maternal factors also may influence some alcohol-related fetal injuries. For example, the risk for FAS increases with the mother's age and with the number of prior pregnancies.

Studying the role of prostaglandins (important hormone-like substances in the body) in increasing the risk of alcohol-induced fetal injury is another consequential area of FAS research. In animal studies, scientists have shown that the severity of alcohol-induced injury to the fetus lessens when drugs that prevent an increase in prostaglandin levels are given prior to alcohol. Because prostaglandins are known to play a key role in fetal development, it is conceivable that alcohol produces injury to the fetus by altering prostaglandin levels. More research is needed in this area to obtain a definitive understanding of the general relationship between hormones and fetal development. This knowledge will help to improve pregnancy outcome in general, as well as to prevent alcohol-related fetal injury.

Alcohol researchers are continuing to explore the fundamental question of how alcohol may directly injure the developing fetus. Although more research is needed to fully understand such effects, scientists are beginning to identify the processes involved in alcohol-induced fetal injury. Currently, studies have shown that fetal exposure to alcohol affects the hippocampus, a region of the brain that is critical to learning and memory. The hypothalamus, a brain area important to the regulation of hormones and behavior, also appears to be vulnerable to the injurious effects of alcohol. Such injuries may result from alcohol's disruption of the timing of nerve cell development, which causes errors in the migration of the cells from their place of origin to their

appropriate location in the mature central nervous system. Research conducted over the next few years may reveal how this disruption of nerve cells leads to changes in the brain that can profoundly affect intellect and behavior.

Animal models have enabled scientists to identify and characterize many of the harmful effects of alcohol on fetal development. Their use in studies analyzing the effects of alcohol on immune system functioning has provided intriguing findings. For example, animal studies have revealed that immune system functioning is impaired and hormonal response to stress is reduced in offspring exposed to alcohol prenatally. These preliminary findings suggest that children exposed to alcohol before birth may have increased susceptibility to infection and delayed healing.

Genetic Vulnerability to FAS and FAE

Although women who drink heavily during pregnancy are at risk of giving birth to babies with FAS, not all who consume alcohol will deliver a child with the syndrome. The incidence of FAS also differs among ethnic groups; both Native American and African-American populations have a higher incidence of the syndrome than other populations. Although the reasons for this variability are not understood fully, genetic factors are believed to influence vulnerability to both FAS and FAE.

Studies of alcohol use and pregnancy outcome have demonstrated that African-American children exposed to alcohol prior to birth are more vulnerable to FAS than the offspring of non-African-American women, despite similar maternal drinking patterns and identical status among the mothers on a number of other key factors, including nutrition. This suggests that a factor present in the African-American population may be responsible for the heightened occurrence of FAS.

One promising explanation involves the metabolic enzyme alcohol dehydrogenase (ADH). The rate at which alcohol is metabolized differs among various ethnic groups and can be influenced by the variant form of ADH expressed in an individual. At present, three variant forms of ADH have been found: beta 1, beta 2, and beta 3. The beta 3 ADH variant has been found in approximately 27 percent of the African-American population; beta 3 is rarely found in other ethnic groups. Preliminary evidence suggests that the beta 3 form of ADH may be found at an even greater frequency in children with FAS. Although this finding must be analyzed further, it may provide a foundation from which scientists can learn more about susceptibility for alcohol-related fetal injury.

Genetic factors are believed to influence vulnerability to both FAS and FAE.

Over the next several years, scientists will continue to explore and define the direct and indirect means by which alcohol can cause harm to unborn children. Future studies are needed to assess the long-term impact on children's behavior and learning. As a future goal, researchers are trying to develop strategies and methods to help children overcome the deficiencies that result from alcohol-induced prenatal injury. These are important challenges to alcohol researchers in the coming decade, because the results will be critical to our future generations.

Until now, research has focused on the potential harm that maternal drinking poses to the fetus. However, recent work suggests that paternal drinking also may pose some risks to the fetus and that these risks are likely to be distinct from those associated with maternal drinking. Although this information is preliminary, it represents an important area for future investigation.

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GOVERNMENT WARNING:
GOVERNMENT WARNING: (1)ACCORDING TO THE SURGEON GENERAL, WOMEN SHOULD NOT DRINK ALCOHOLIC BEVERAGES DURING PREGNANCY BECAUSE OF THE RISK OF BIRTH DEFECTS. (2)CONSUMPTION OF ALCOHOLIC BEVERAGES IMPAIRS YOUR ABILITY TO DRIVE A CAR OR

BEST COPY AVAILABLE

VII Prevention and Treatment

The overriding aim of all alcohol research is to produce knowledge that will enhance our ability to prevent alcoholism, alcohol abuse, and associated problems and to treat alcoholism. In each of the areas of alcohol investigation highlighted in the preceding chapters, scientists generate such knowledge by exploring new research questions; by replicating, or repeating, promising experiments both to verify results and to determine the extent of their utility; and by applying advanced experimental designs and technologies to reveal previously inaccessible information.

Like their counterparts in other areas of alcohol studies, many prevention and treatment researchers concentrate on gathering basic knowledge for developing or enhancing prevention and treatment strategies. Others, called applied researchers, test the effectiveness of these strategies as they are implemented in "real-world" settings—a task that is especially challenging because, in the real world, behavior may be influenced by many factors other than the strategy being evaluated.

To control for these confounding factors, scientists during the past decade incorporated rigorous experimental designs such as controlled clinical trials, experiments that attempt to determine a treatment's effects in a manner that is unbiased by external factors. In addition, they applied innovative designs such as time-series analysis, a technique that allows the analysis of multiple factors over time, and advanced technologies such as computer simulation to examine the many factors that can influence the development—and the reduction—of alcohol abuse, alcoholism, and related problems.

With these methodological advances, scientists revealed new information about the range of social,

Research currently is being conducted to assess the efficacy of warning labels on alcoholic beverage containers as a prevention measure. Photograph courtesy of Stacey Hudson.

psychological, and economic characteristics present among alcohol dependent persons and about the relationship of these characteristics to treatment outcome. At the same time, they began to consider multiple factors—including medical, social, and economic factors—together with drinking behavior as measures of treatment outcome. These new directions brought scientists to the brink of concerted efforts to resolve the most pressing need in treatment research: To define which treatments are most beneficial for which types of patients. Expanding these efforts is a central focus of alcohol research during the 1990s.

Across the past decade, researchers also gathered new information that documents the range and complexity of alcohol-related problems throughout society. As the effects of drinking on a host of physical and social problems (including injuries, disease, violence, homelessness, unemployment, marital discord, and others) became increasingly apparent, the focus of prevention extended beyond preventing alcoholism to preventing consequences of alcohol use, including single episodes of alcohol abuse. These developments were facilitated by improved measurement of alcohol-related problems, improved research design, and sophisticated theoretical and conceptual models of the systems of alcohol use that give rise to physical and social problems.

These methodological and conceptual advances will be critical for meeting the challenges of a decade that promises to produce a wealth of new information for further enhancing prevention and treatment effectiveness.

Prevention Research

Alcoholism and alcohol-related problems are believed to result from an interaction of individual and environmental factors. During the past decade, prevention researchers worked to identify the individual factors that can place a person at risk and the environmental factors that can affect that risk. Further, they explored the interactions among these individual and environmental factors, with the aim of identifying opportunities to prevent the onset of alcohol-related problems and the onset of alcoholism.

Identifying Risk and Vulnerability

Scientists studying individual vulnerability initiated studies to measure demographic, biological, and psychological variables—including gender, family history, neurophysiological characteristics, temperament, personality, behavior, and social interactions—in large samples. One such study, initiated in 1989, is the multisite collaborative search for the gene or genes responsible for alcoholism.

Social learning theory is being used to explore whether changing drinking-associated thoughts or activities can prevent problematic drinking behavior.

expected during the 1990s to report results that will provide insights into the etiology and developmental course of different types of alcoholism. Results of the genetics collaboration and the entire genetics research agenda during the next decade should enable health care workers eventually to identify persons who are genetically at risk for alcoholism and to provide appropriate preventive interventions.

In addition to genetic risk for alcoholism, researchers are focusing on individual factors that contribute to risk for alcohol-related problems. Studies of life-course development are underway to determine how individual physiological and psychological factors interact with early life events to produce risk for alcohol-related problems at various developmental stages, including adolescence. Social learning theory, which delineates the processes by which individuals acquire and maintain behavior, is being used to explore whether changing drinking-associated thoughts or activities can prevent problematic drinking behavior. Among social learning approaches that evidence promise for alcohol-problem prevention are cognitive restructuring, an approach that modifies beliefs or expectancies about appropriate drinking behavior, and coping skills training, an approach that teaches new habits for exercising self-control when drinking. During the next decade, researchers will focus on identifying promising targets for such interventions and on understanding their mediating mechanisms.

Another aspect of understanding behaviors that lead to alcohol problems involves understanding the contribution of environmental factors. During the past decade, researchers focused on identifying environmental factors that affect only a few individuals (for example, selected families, peer groups, and work settings) and factors in the broader societal culture that affect many individuals (for example, price and availability of alcohol, advertising, and media portrayals of drinking). Objectives for research during the next decade include developing effective measures for modifying environmental risk and

testing the effectiveness of selective modifications.

Targeting Adverse Consequences of Drinking

An area of prevention research already focusing on the interaction of individual and environmental factors is the study of adverse consequences of drinking. Researchers studying alcohol-related accidents, trauma, crime and violence, and a possible association between alcohol and AIDS are gathering essential baseline information about individual and environmental risk factors and their interaction. Other researchers are testing the effectiveness of specific efforts to modify those risks. Some research directions related to alcohol-impaired driving and to alcohol and AIDS illustrate the importance of this work.

Drinking and driving. Current data show that the percentage of drivers who were intoxicated in fatal crashes decreased by 18 percent from 1982 through 1988. This declining trend was especially evident among teenage drivers, who experienced a 36-percent decrease in the proportion of drivers who were intoxicated in fatal crashes. However, analysis based on a per-miles-driven measure demonstrates that alcohol nevertheless is involved in a disproportionate number of fatal crashes among teenage drivers relative to other age groups. Among plausible reasons for this disparity are teenagers' relative inexperience with both drinking and driving, inadequate school-based educational programs, and teenagers' ability to circumvent minimum purchase age laws. Consequently, researchers continue to gather information about individual (for example, drinking frequency among young drivers) and environmental (for example, access to alcohol) risk factors among young drivers and to explore the effectiveness of measures designed to reduce individual risks (for example, license sanctions for alcohol use) and measures designed to reduce environmental risks (for example, restricted access to alcohol) among this population. In addition, they continue to assess the effects of minimum-drinking-age legislation, as well as community and grassroots organizational efforts to reduce drinking and driving.

Another environmental strategy for preventing alcohol-impaired driving is server intervention, developed by the hospitality industry to reduce the likelihood that alcohol is served to underage or visibly intoxicated persons. Server intervention incorporates legislation (dram-shop laws), education (server training), and changes in the context in which alcohol is served (for example, time-of-day, drinking occasion, food-service practices) to modify environmental risk. In conducting studies of server-intervention, researchers will gather basic information about public drinking and drinking contexts and identify the most effective service policies and programs to modify both individual and environmental risks. Because the majority of driving-while-intoxicated offenders do most of their drinking in bars, it is important to determine the contribution of drinking site to alcohol-related problem outcomes.

Alcohol and AIDS. Scientists have shown that alcohol consumption affects the body's immune function. Researchers are exploring whether alcohol consumption in persons who are HIV-infected may contribute to the progression to AIDS or to increased severity of immune dysfunction associated with AIDS.

Psychosocial research has shown that alcohol use can influence sexual behavior, and the findings of some studies suggest that alcohol use may increase high-risk sexual behavior. An

exploratory study conducted in San Francisco, California, reported that homosexual men were less likely to use condoms following drinking or drug use, and a Massachusetts survey of adolescents and adults reported that heterosexual respondents who averaged five or more drinks daily were less likely to use condoms than their peers who drank less.

Although we do not know that alcohol use contributes to increased risk of HIV-infection or to the development of AIDS, the threat posed by the AIDS epidemic demands that scientists continue to explore any possible biological effects of alcohol use on HIV infection and AIDS. In addition, the AIDS crisis demands that researchers seek new information about the role of alcohol in risk-taking behavior and about alcohol use as a coping behavior in individuals with high-risk or HIV-positive status.

Refining Research Technology

Among the new tools to assist research on drinking and driving and other prevention strategies is computer simulation—an approach that, unlike conventional statistical techniques, can be used to analyze dynamic social and economic environments in which many factors interact over time. Planners in San Diego, California, recently used computer simulation to document the extent of alcohol-involved traffic problems, understand the complex system in which the problems occur, and project the effects of various prevention strategies on reducing alcohol-involved traffic problems.

Together with such new technologies as computer simulation, prevention research during the next decade will rely on several proven experimental designs that have developed over time. Many areas of alcohol research have contributed research designs that help to isolate individual and environmental risk factors and to explore their interactions. For example, family studies of the past decade produced procedures for measuring important family variables and generated hypotheses relating certain variables to alcohol abuse among the children of alcoholic parents. From this work evolved such technologies as multiple cohort studies, multigenerational designs, and refined longitudinal studies—all of which will be used in the next decade to examine the effects of individual and environmental family factors in the development and perpetuation of alcoholism and alcohol-related problems.

In addition, researchers will use sophisticated prospective studies to enhance understanding of the etiology of alcohol problems and prevention trials to test the effectiveness of specific interventions. Because prevention trials can target and intervene with a presumed risk factor in a healthy population, this approach allows for experimental manipulation that will enhance the value of the research. Prevention trials also can produce information about etiology by testing causal theories.

In addition, researchers will avail themselves of natural experiments (for example, changes in zoning laws governing alcohol sales) to observe the effects of specific environmental interventions. Natural experiments can produce information that is both realistic and socially relevant and of immediate practical utility.

Evaluating Prevention Strategies

As noted, applied prevention researchers assess the effectiveness of purposeful actions designed to change individual behaviors (educational programs, for example) and measures designed to modify the drinking environment (minimum-drinking-age legislation, for example). Some focal areas of study for the early 1990s include school-based and community programs, the impact of alcohol-warning labels, and worksite programs.

School-based and community programs. Researchers have shown that promising techniques for health promotion include targeting individuals and groups at risk, imparting skills necessary for behavior change, exerting multiple strategies simultaneously, and timing prevention messages to achieve maximum effects.

In addition, they have found that school-based prevention programs based on social learning theory show promise for reducing alcohol use among young people. Social learning programs can teach drink-refusal skills, correct inaccurate expectations about alcohol's effects, and alert young people to misleading messages contained in advertising and media portrayals of alcohol use. Most of these programs emphasize the role of peers in influencing drinking behavior. During the 1990s, researchers will develop and refine the social-learning approach, test new school-based approaches, and determine the most effective match of age group and prevention approach.

In addition, prevention science has advanced to the point that is appropriate to develop prototypes for comprehensive community programs to prevent underage drinking, drinking and driving, and alcohol use during pregnancy and to test those programs in long-term community trials. Community trials in other areas of health promotion and disease prevention have shown that the potential exists for beneficial, synergistic effects when several approaches are combined. Accordingly, alcohol researchers during the 1990s will evaluate the feasibility of such trials for alcohol-problem prevention, pilot test

program components, and develop and initiate prototype programs.

Alcohol-warning labels. Public Law 100-690, which required that warning labels be placed on all containers of alcoholic beverages, created an opportunity to assess the impact of such labels on public knowledge, attitudes, and behavior. The findings of research to evaluate the effectiveness of warning labels on nonalcohol products suggest that the effectiveness of the labels may depend on such factors as characteristics of the labels and characteristics of the population to which the warnings are directed.

During the next decade, prevention researchers will assess the impact of warning labels on alcoholic beverages in different situations (including situations in which several preventive actions are used simultaneously and situations in which competing messages favoring consumption are present) and in different populations. Moreover, they can compare drinking behavior before and after labeling and can measure actual reductions, if they occur, in alcohol-impaired driving and drinking during pregnancy

Worksite programs. During the past two decades, numerous strategies have been developed that aim, either directly or indirectly, to prevent the occurrence of alcohol abuse or alcoholism in employees (for example, health promotion programs, quality of work life programs) or to prevent the progression of such problems when they exist (for example, screening and testing programs, employee assistance programs). Although some research has been conducted on the effectiveness of employee assistance programs, additional, methodologically advanced research will be required during the next decade to assess the relative effectiveness of various types of programs for reducing alcohol-related problems and enhancing worker productivity, especially among such employee subgroups as women and ethnic minorities. Also needed is research to assess the impact of screening and testing on business costs, worker morale, turnover, and productivity.

Few studies have examined how the workplace may contribute to the development of alcohol abuse, alcoholism, and related problems. Consequently, researchers during the next decade also will gather basic information about worksite factors, worker factors, and their interactions that may increase or decrease the incidence, duration, and severity of alcohol problems in the workplace.

Some focal areas of study for the early 1990s include school-based and community programs, the impact of alcohol-warning labels, and worksite programs.

TREATMENT RESEARCH

The strategies discussed earlier in this chapter are aimed at preventing the onset of alcoholism, alcohol abuse, or alcohol-related societal problems or at preventing some combination of those problems. In contrast, most treatment strategies are designed specifically to ameliorate alcoholism—the most severe alcohol problem—when it occurs.

Like optimal prevention strategies, optimal treatment strategies are facilitated by a strong research base. Central components of this research base include investigations that measure patient factors, treatment factors, and their relationship to treatment success and investigations that assess the efficiency with which treatment services reach persons in need of those services.

Over the past two decades, researchers showed that alcoholism treatment contributes to prolonged abstinence in some patients. However, they also showed that most patients experience at least one relapse to drinking following treatment. It remains to be determined why some patients begin a period of permanent or prolonged abstinence immediately following alcoholism treatment whereas others become abstinent at a later time or not at all. Also to be determined is whether treatment produces benefits in other areas of social or psychological functioning for patients who do not immediately achieve abstinence.

To better understand the benefits of alcoholism treatment and to improve the percentage of patients who experience those benefits, researchers are working to define the active ingredients of various treatment strategies and to determine which patient factors influence treatment outcome. Related efforts include refining diagnostic classifications of alcoholism; developing improved tools for screening, diagnosis, and assessment; and improving treatment outcome evaluation. As a result of these activities, researchers can make important advances toward defining reasonable goals for specific interventions and determining the best treatments for specific patient types.

Further, researchers are working to provide information that will help to ensure that treatment services reach the population in need of treatment. During past decades, researchers found that general medical expenditures by alcoholics and their families are reduced substantially following alcoholism treatment. In addition, the benefits derived from treating alcoholics were shown to offset costs to the general health care system. In light of these findings, efforts during the next decade will focus on expanding information about the capacities, quality, availability, utilization, and costs of alcoholism treatment services in relation to the need and the demand for those services.

Also during the next decade, researchers are expected to uncover new knowledge of genetic factors in alcoholism; brain actions and mechanisms involved in reinforcement, tolerance, dependence, craving, and relapse; and alcohol-associated medical consequences. Translating this new knowledge into improved psychological and pharmacological interventions and ensuring that those interventions reach persons in need are among the most important challenges of the 1990s.

Research on typologies can provide important information for understanding both the causation and expression of various types of alcoholism.

Screening and Diagnosis

Researchers have developed a number of easily and inexpensively administered screening procedures to identify persons who have begun to develop or are at risk of developing alcoholism. The most commonly used screening tools are self-reports and structured interviews, both of which may be supplemented by laboratory tests designed to detect physiological changes often associated with excessive alcohol consumption.

Although most screening tools were developed to identify active cases of alcoholism, others are being developed to identify individuals who are at increased risk for the disease. During the next decade, researchers will continue to develop and evaluate low-cost, rapid screening procedures that can be used routinely in primary health care, educational, and other settings.

Resources also are being targeted to further the development of diagnostic procedures that will provide more—and more valuable—information for clinicians. These include diagnostic mechanisms that enable classification according to severity of alcohol dependence. Mechanisms such as the Addiction Severity Index, the Diagnostic Interview Schedule, the Alcohol Use Inventory, and the Inventory of Drinking Situations generate reliable, standardized scores that are useful in treatment planning and treatment research. Research during the next decade should improve diagnostic specificity, thus enabling clinicians to design treatment plans that take account of each alcoholic's physical, psychological, and social characteristics, as well as drinking pattern.

Biochemical Markers of Alcohol Consumption

At present, most physicians base a diagnosis of alcoholism on a patient's description of past alcohol consumption patterns and current self-reported problems with alcohol. Although helpful, this information, at times, is incomplete or inadequate.

Identifying specific, sensitive, and practicable biochemical markers of alcohol consumption is a major research goal for the 1990s. The ideal marker would objectively identify heavy alcohol consumption and alcohol dependence, thus assisting physicians in accurately identifying patients who are alcohol abusers or alcoholics, optimally before the onset of serious drinking-related medical or social consequences. In addition, the ideal marker would identify low levels of consumption, thus also enabling treatment personnel (and, when applicable, investigators conducting clinical research) to monitor abstinence during and following alcoholism treatment.

Although such a marker is not yet at hand, researchers have identified several promising candidates. These candidates range from several liver enzymes, to modified blood proteins, to the physical appearance of red blood cells.

Patient-Treatment Matching

Over the past decade, researchers have discovered that patient characteristics can be predictive of treatment outcome and that patients with certain characteristics appear to respond better to certain treatment formats, settings, and levels of intensity. In addition, research findings show that selectively matching patient characteristics to treatment characteristics can improve treatment outcome.

A large, multisite clinical trial now underway is expected during the next decade to identify a range of promising interactions between patient characteristics and treatment characteristics. This collaborative study employs large, representative sample groups, thus allowing for sophisticated statistical analyses and ensuring that results will be generalizable to a variety of alcoholism treatment programs. The patient-treatment matching study will measure treatment effectiveness from a cost perspective as well as a clinical perspective, thus producing information to improve both treatment effectiveness and treatment efficiency.

Simultaneous with this study, researchers will continue to differentiate typologies, or subgroups, of alcoholics according to clusters of shared traits. Research on typologies can provide important information for understanding both the causation and expression of various types of alcoholism. Such typologies also should have important implications for patient-treatment matching.

PERFORMANCE RESEARCH UNITS
NIAAA Patient-Treatment Matching

Project Match is a large clinical study being conducted at nine clinical research sites throughout the country. The goal of this project is to identify a range of promising interactions between patient characteristics and treatment approaches. Courtesy of Dr. Margaret Mattson.

Treatment Outcome Evaluation

Alcoholism treatment outcome research in recent years has incorporated many refinements in study design, methodology, and analysis. Among these improvements are random sample selection, the use of controls, methods for corroborating self-reports of drinking behavior, multiple and objective measures of treatment effects, adequate followup, and sophisticated statistical analyses.

Despite these accomplishments, however, scientifically rigorous outcome research remains challenging due to the complexity of alcoholism treatment itself. For example, patients usually are exposed to multiple interventions and multiple caregivers within a single treatment setting—a situation that creates difficulty in measuring the independent effects of any single treatment component.

Accordingly, assessment of treatment process—that is, the specification of events or factors that may facilitate or impede the success of therapeutic activities—will become an important research issue during the coming decade. Researchers will explore factors that influence a patient's decision to seek treatment, remain in treatment, comply with program requirements, and accept referrals. Additional factors may include treatment program duration, counselor characteristics, and treatment integrity (the consistency with which specific therapies are delivered). Information about how variations in treatment process affect outcome will provide important information for enhancing treatment services.

Health Services Research

Health services research develops knowledge of the capacities, quality, availability, utilization, and costs of alcoholism treatment services. During the 1990s, researchers will perform highly systematic evaluations of alcoholism treatment as it is now structured and will collect cross-sectional data on treatment populations, including prior treatment history, extent of impairment, sociodemographic factors, and other characteristics. Such comprehensive studies have the potential to provide information

Research is focused on improving alcoholism treatment by enhancing current strategies and by developing and testing new approaches.

about access to treatment, referral patterns, payment sources, services received, treatment participation, and assessment techniques that can assist effective program planning at the Federal, State, and local levels.

Through health services research, investigators also have the potential to measure hospital use and costs for patients who are alcoholic and to explore the distribution of health conditions associated with alcoholism.

Innovative Treatments

Even as research progresses toward understanding the brain processes involved in alcohol craving and reinforcement and toward developing appropriate pharmacological interventions, researchers have devised several nonpharmacological strategies designed to diminish, forestall, or attenuate the threat of relapse. Existing relapse-prevention strategies fall into two general categories: (1) cognitive-behavioral strategies, which are designed to alter a sequence of cognitive and behavioral events that may lead to relapse, and (2) cue-exposure strategies, which are designed to diminish alcoholics' responses to cues (for example, the sight or smell of alcohol or negative mood states) that may precipitate the desire to drink.

Much research remains to be done to determine whether relapse-prevention strategies significantly affect the severity, frequency, or duration of posttreatment relapses and which strategies are most effective for specific populations at which points in the treatment process. For example, some cognitive-behavioral strategies that have been used only with alcohol abusers may be ineffective with alcoholic patients or may be effective for use only after patients complete a traditional alcoholism treatment program. To resolve these questions, further exploration of relapse-prevention strategies is warranted.

The next decade will produce a host of new pharmacological and nonpharmacological interventions based on findings in the burgeoning areas of genetics, neuroscience, and other areas of investigation. The promise of the coming decade is that each discovery brings with it the hope of resolving alcohol problems in individual lives and throughout our society.

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Focus on Developing New Medications for Alcoholism

Scientists have made great strides toward understanding how alcohol acts on numerous networks in the brain to exert its effects. This knowledge has launched a burgeoning era of research efforts to develop medications that act on brain networks to impede the progression of alcoholism and lessen the risk for relapse to the disease.

Because of the complex nature of alcoholism, it is unlikely that a single pharmacological agent will be developed to treat this disease. Rather, researchers are concentrating on developing agents to manage the specific events that occur in the clinical course of alcoholism and complicate the recovery process. These new medications can improve long-term treatment outcome when coupled with traditional verbal and behavioral therapies. Research efforts are focused on developing pharmacological agents to:

- Modify drinking behavior to control craving and prevent relapse
- Induce sobriety in intoxicated patients
- Improve mental abilities in patients with alcohol-induced cognitive deficits
- Manage acute alcohol withdrawal
- Treat the protracted withdrawal syndrome
- Decrease alcohol consumption by treating coexisting psychiatric disorders.

Controlling Craving and Preventing Relapse

The recognition that certain pharmacological agents may reduce the desire for alcohol is one of the most exciting developments in pharmacotherapy and has launched a new area of research for developing medications. Pharmacological agents may reduce

Research is ongoing to develop different classes of medications to treat the various aspects of alcoholism. Photograph by Scott Sinklier, Pioneer Hi-Bred International, Inc.

the desire for alcohol in a variety of ways. By decreasing craving, by blocking the reinforcing effects of alcohol, or by producing aversive reactions when combined with alcohol, these agents can help to prevent relapse to drinking.

A number of neurotransmitter systems influence an individual's response to alcohol and underlie alcohol-seeking behavior. Research findings suggest that diminished levels of serotonin, a brain neurotransmitter that affects mood and consummatory behavior, may influence the appetite for alcohol. Accordingly, scientists have begun to evaluate a promising new group of drugs, known as serotonin uptake inhibitors, that act to enhance brain serotonin activity. These agents may reduce consumption by abating the desire or craving for alcohol experienced by many alcoholic individuals. The use of these agents during the early stages of recovery, when craving for alcohol can be extreme, may help the recovering individual progress through this stage and continue treatment.

Several of these drugs successfully have decreased alcohol consumption in experimental animals. In studies with voluntary human participants, one of these drugs, citalopram, caused alcoholic individuals to consume less alcohol and remain abstinent for a greater number of days.

The serotonin uptake inhibitors currently available have an important limitation: People can become tolerant to their effects within a brief time period. Nevertheless, the positive results obtained from recent studies indicate that, in the coming decade, researchers may be able to design analogs of these pharmacological agents with long-term potential for mitigating the craving or appetite for alcohol.

A different class of drugs with potential for reducing alcohol consumption is represented by the prototype agent buspirone. Drugs from this class usually are used to treat anxiety; thus, these agents may prove to be effective in alcohol treatment, particularly among alcoholics who recently have become abstinent and are experiencing high levels of anxiety. Although buspirone is not considered a serotonin uptake inhibitor, researchers believe that its ability to increase brain serotonin activity may account, in part, for its potential therapeutic effects.

Dopamine, another neurotransmitter influenced by alcohol consumption, may play a role in the expression of the alcohol-induced euphoria that appears to reinforce continued drinking. Pharmacological agents that mimic dopamine, such as bromocriptine, may lessen craving and drinking in dependent persons by blocking this reinforcing effect.

Naltrexone is an opiate antagonist—a substance that inhibits or blocks the action of agents that activate the opiate receptor—that has reduced alcohol consumption in humans and animals in precursory studies.

The neurotransmitter gamma-aminobutyric (GABA) also influences drinking behavior. Although the results are preliminary, the GABA receptor agonist calcium bis acetyl homotaurine—an agent that mirrors the actions of GABA when it binds to the GABA receptor—has increased abstinence in alcoholics during a 3-month experimental period.

Other medications show significant promise in their ability to suppress alcohol consumption. Naltrexone is an opiate antagonist—a substance that inhibits or blocks the action of agents that activate the opiate receptor—that has reduced alcohol consumption in humans and animals in precursory studies. Nonetheless, further study is needed to determine naltrexone's mechanism of action.

Aversive Agents

Other medications reduce drinking not by acting directly on the central nervous system but by causing unpleasant effects when combined with alcohol. Disulfiram (Antabuse), a medication used in alcoholism treatment for more than 40 years, acts by blocking the activity of one of the primary enzymes responsible for alcohol metabolism. The unpleasant reaction results from a rise in the noxious alcohol metabolite acetaldehyde when alcohol is consumed. However, because patients who have difficulty complying with medication regimens may not benefit from disulfiram therapy, researchers are seeking other aversive agents that may be more practical for a number of patients.

Inducing Sobriety in Intoxicated Patients

Alcohol produces its effects by influencing a myriad of brain systems, making it difficult to find a single agent that reverses its intoxicating effects. Currently, researchers are focusing on a range of medications that counteract specific aspects of intoxication (amethystic agents). Although the available agents do not lessen the toxic effects of alcohol on

the body or modify drinking behavior, they can be useful in certain life-threatening conditions.

An experimental benzodiazepine compound called Ro15-4513, which appears to block several of the intoxicating effects of alcohol, has produced promising results in animal studies. However, because this agent produces anxiety and promotes seizures, it cannot be used with humans. Nonetheless, the findings on Ro15-4513 suggest that some of the pharmacologic properties of alcohol can be inhibited with the development of safe pharmaceutical agents. These findings lay the foundation for enhanced research efforts in the coming decade to develop new medications that induce sobriety.

New areas of research on the molecular biology of the brain may generate dramatically new approaches to the pharmacologic treatment of alcoholism. Photograph courtesy of Genex.

Treating Alcohol-Induced Cognitive Impairments

At present, verbal, psychological, and cognitive therapies remain the most effective forms of alcoholism therapy. However, cognitive deficits, which are a consequence of years of alcohol abuse, may interfere with a patient's capacity to learn (that is, to form new memories)—a necessary ability in alcoholism therapy. This pathological consequence of alcoholism may influence an alcoholic patient's capacity to succeed in treatment.

Pharmacological agents that enhance the recovery of brain function may offer a patient the potential to better benefit from traditional treatment approaches. The severity of cognitive impairment can vary among alcoholic patients; the most extreme damage is observed in alcoholics with Wernicke-Korsakoff's syndrome, who have amnesia for recent events and an inability to form new memories. Recently, clinical researchers using a drug called fluvoxamine have observed some memory improvement in patients with Wernicke-Korsakoff's syndrome. This drug acts by increasing the levels of the neurotransmitter serotonin in brain nerve cells. Agents that act on the serotonin system offer exciting potential as medications to augment and restore cognitive function in alcoholic patients.

Clonidine, a pharmacological agent that affects norepinephrine, also appears to provide some benefit to alcoholic patients with impaired cognitive function. The findings on fluvoxamine and clonidine suggest that pharmacological agents within their respective classes can be developed as effective medications for patients with less severe, reversible cognitive impairments.

These preliminary results have encouraged researchers in their search for medications to improve alcohol-induced mental deficits. Because these deficits limit the daily functioning of impaired individuals and interfere with their ability to benefit from alcoholism treatment, the development of

new medications to improve cognitive function is a primary issue of alcohol research in the coming decade.

Managing Acute Alcohol Withdrawal

Managing alcohol withdrawal is the first step in alcoholism treatment. Proper treatment for withdrawal can help a patient to become detoxified in a safe and comfortable manner and, further, can foster the patient's motivation to enter rehabilitation therapy.

The body adapts to heavy and habitual drinking by counteracting the depressant effects of alcohol: Excitability of the brain increases in an effort to "normalize" brain function. When an individual abruptly stops drinking, however, the depressant effects of alcohol also cease and the adaptive increase in brain excitability becomes maladaptive. This maladaptive hyperexcitability of the brain is the basis for acute alcohol withdrawal syndrome, with symptoms ranging from restlessness, anxiety, tremors, irregular heart rhythm, and elevated blood pressure to more severe consequences such as seizures. Delirium tremens, a life-threatening stage of withdrawal that involves profound confusion, hallucinations, and severe nervous system overactivity, also may develop.

Although the severity of withdrawal symptoms varies from one person to another, recent findings suggest that it may be important to treat everyone who is suffering from alcohol withdrawal, regardless of symptom severity. Inadequate treatment may lead to more serious withdrawal episodes in the future. Moreover, repeated untreated withdrawals from alcohol may cause damage to the part of the brain thought to be important for memory and control of emotion.

For more than two decades, benzodiazepines such as diazepam (Valium) have been the medications of choice for treating alcohol withdrawal. These benzodiazepines are anticonvulsive agents that inhibit brain cell activity, thus preventing the onset of seizures. These medications also counter such symptoms as elevated blood pressure, irregular heart rhythm, and tremors.

As we learn more about the physiological mechanisms involved in alcohol withdrawal, it becomes possible to test new medications that expressly control these processes. For example, research findings have revealed that the production of the neurotransmitter norepinephrine—a chemical messenger associated with functioning of the sympathetic nervous system—increases during withdrawal. This knowledge has energized the search for pharmacological agents that can counteract this process. Two such agents, atenolol and propranolol, used as adjuncts to benzodiazepines, have shown promise for alleviating tremors and heart rhythm irregularity. Further, atenolol appears to resolve the anxiety, agitation, and hallucinations that may accompany withdrawal; yet, it also appears to stimulate processes in the body responsible for other withdrawal symptoms.

Studies exploring the underlying mechanisms involved in protracted withdrawal and its relation to relapse will be an important focus of research efforts in the coming decade.

Two other drugs that act on norepinephrine—clonidine and lofexidine—have been tested in clinical settings. These drugs (which suppress the release of norepinephrine) have been found to control tremors, elevated blood pressure, and heart rhythm irregularity. However, they are less effective in alleviating restlessness and insomnia and their usefulness in preventing seizures and delirium tremens has not been established.

Many of these findings are preliminary. Future research will determine the full potential of all of these pharmacological agents—including analogs of these drugs and newly designed agents—as medications for treating severe forms of withdrawal.

Research conducted in the past 10 years has provided a greater understanding of the physiological processes involved in alcohol withdrawal, knowledge that can be applied in the search for new medications to manage withdrawal. The discovery of agents that act on different sites and produce different yet complementary effects can help to treat the complex symptoms of alcohol withdrawal and hasten a patient's entry into rehabilitation therapy.

Treating the Protracted Withdrawal Syndrome

As noted, alcoholic individuals can experience insomnia, anxiety, irritability, fatigue, and depression during the first days of abstinence. When milder forms of these symptoms persist for several weeks or months, however, they indicate the development of a condition known as protracted withdrawal syndrome. Protracted withdrawal may contribute to relapse through two independent mechanisms. First, alcoholics may return to drinking in an effort to ease the discomfort of its symptoms. Second, the symptoms of protracted withdrawal may interfere with treatment progress

by preventing an individual from focusing on therapy.

Although this syndrome is not well understood, researchers have found that its symptoms have a physiological basis. The hyperexcitability of the brain that is observed during acute withdrawal can continue long after an individual stops drinking.

Although limited progress has been made toward developing medications for protracted alcohol withdrawal, experience with treatments for other drug addictions is encouraging. For example, some medications in the antidepressant class appear to lessen symptoms of protracted withdrawal among cocaine dependent persons.

Studies exploring the underlying mechanisms involved in protracted withdrawal and its relation to relapse will be an important focus of research efforts in the coming decade. These studies will provide the basis for developing medications to treat protracted withdrawal symptoms.

Treating Coexisting Psychiatric Disorders

Alcoholics often display symptoms associated with such psychiatric disorders as depression, anxiety, manic-depression, and antisocial personality. Some of these symptoms may result from the acute and chronic effects of alcohol consumption. In some cases, however, the symptoms suggest a coexisting psychiatric problem.

Some alcoholics use alcohol to alleviate psychiatric symptoms. In addition, alcoholism directly or indirectly may increase the risk for developing certain psychiatric problems. Regardless of the basis of the drinking or the psychiatric symptoms, researchers are trying to determine the effect that treatment of a coexisting psychiatric problem may have on drinking outcome. New medications to treat psychiatric disorders also may be effective for treating alcoholism. Conversely, medications used to treat alcoholism may prove to be useful in treating coexisting psychiatric disorders. Continuing investigations of the relationship between alcoholism and coexisting psychiatric problems will be critical for the treatment of both alcoholism and associated psychiatric disorders.

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EPILOG

As we begin a new era in alcohol research, we are inspired by the impressive progress made in the field over the past 20 years. Today, the knowledge gained from prior studies is providing researchers with a sound framework for understanding the causes and consequences of alcohol abuse and alcoholism. Despite our many advances, however, these disorders continue to be devastating and costly health problems that affect millions of individuals.

The seriousness of alcohol problems is heightened by the limited results obtained from current treatment measures for alcoholism. Although current approaches promote prolonged abstinence in some patients, the rate of relapse to drinking is still too high. It is only through research that we can construct effective treatment strategies that will help those overwhelmed by the power of alcohol addiction to achieve long-term sobriety. Scientists within the many biomedical and psychosocial disciplines of the alcohol field are working collectively toward this goal. Their concerted efforts to gain additional knowledge of the effects of alcohol on the body, the nature of addiction, and the genetic and environmental factors that increase the risk for alcoholism and related medical pathologies will bring us closer to conceiving effective methods for alcoholism treatment.

Central to this pursuit are studies aimed at developing new medications to treat alcoholism. In the coming decade, researchers will be searching for pharmacological agents that act on brain networks to impede the progression of alcoholism and lessen the risk for relapse. Although it is doubtful that one agent can be developed to treat this disease, there is promise that pharmacological treatments coupled with traditional behavioral therapies can improve long-term treatment outcome.

Powerful new technologies will open many new avenues of investigation during the next decade. Noninvasive neuroimaging techniques, which offer the unprecedented opportunity to look into the living brain, are enabling scientists to probe the effects of alcohol on brain structures and functions. Tools in molecular biology are facilitating the search for genetic factors that predispose individuals to alcoholism and alcohol-related pathologies. Sophisticated computer models, which analyze the dynamic social and economic environments with which alcohol abuse occurs, are allowing researchers to project potential outcomes of various prevention strategies.

Building upon the strong foundation laid by past findings—and galvanized by new technologies—alcohol researchers will have exceptional opportunities to make new discoveries about alcohol abuse and alcoholism in the coming decade. Technology and increased knowledge will empower researchers to solve many of the unanswered questions in alcohol research and ultimately to effectively prevent and treat alcohol problems. ■